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COMMUNICATIONS

THE DYSTROPHIES OF THE MACULA

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With a genetic note by H. GRÜNEBERG (London)

FAMILIAL occurrence of lesions in the fundus situated mainly or exclusively in the central area has been recorded independently by a number of early observers: Hutchinson in 1875, Lang in 1885, Liebrecht in 1895, Batten in 1897, Haas in 1898, Doyne in 1899, Dujardin in 1904, Best in 1905, and Stargardt in 1909. As long as they constituted isolated observations the intricate problem of the unity of the different appearances shown by the families recorded and the no less complicated problem of the relationship of these cases to those showing familial macular lesions with psychic or neurological disturbances (Tay-Sachs disease and cerebro-macular degeneration) did not arise. Inevitably, incidental observations tended to assume an exaggerated significance in early reports. Thus in Doyne's cases the " honey-comb appearance "—by no means a characteristic feature in some of Doyne's later cases—has dominated the discussions on this affection. Best's belief that in his cases the lesion was congenital and stationary has likewise tended to emphasize features which are probably not valid, but led Stargardt to differentiate his own cases as developing in childhood and showing a progressive course. These difficulties have become less real when subsequent

reports showed that many cases conform to the description given by Stargardt and such of the earlier observers as Batten and Dujardin.* A large group has these unifying features: (1) familial occurrence, (2) a bilateral fundus lesion confined essentially to the macular area, (3) onset at about 8-14 years of age, (4) progressive course leading to loss of central vision and no peripheral involvement.

The recognition of this clear-cut group still leaves the problem of the significance of such " atypical " cases as those of Doyne, of Best and of many other subsequent observers. What contact there is between the " typical " and " atypical " cases can be assessed only when the limits of the more clearly established entity are defined. In recording eight new familial groups, some of them showing considerable departures from the classical type of familial progressive macular degeneration, the literature is reviewed and an attempt is made to classify these affections in relation to each other, to the more recently recognised allied conditions, and to cerebro-macular degeneration. In reviewing the literature, isolated cases, *i.e.*, those in which the diagnosis has been made without a definite family history, have been discarded —except for incidental reference—as lacking conclusive validity for analytical purposes.

(1) The Clinical Varieties of Central Fundus Lesions of a Familial or Hereditary Type

There is a considerable variety of familial affections confined largely or exclusively to the central area of the fundus—some recognised only recently.

(i) *Congenital macular coloboma.*

Familial cases of this congenital and non-progressive lesion were first reported by Schott and by Clausen in 1921. Subsequent reports have come from Davenport (1927), Sorsby (1935), Evans (1937) and Niccol (1938). Direct dominant inheritance was noted by Clausen, Davenport and Sorsby. Sorsby's cases have the additional interest of an associated skeletal defect: apical dystrophy of hands and feet.

(ii) *Best's disease.*

So far the appearances described by Best in 1905 in eight members of one family have not been recorded outside the collateral branches of this particular family. The family originally

* Hutchinson's cases are best left out of any discussion on the subject. The description (devoid of illustrations) is not sufficiently explicit to enable a clear retrospective diagnosis. They can be claimed as examples of familial choroidal sclerosis, " Doyne's Choroiditis " or macular dystrophy.

studied by Best has been the subject of subsequent and exhaustive investigations by Vossius, Weisel and Jung; 22 members out of 300 studied are now known to be affected. Lloyd speaks of having seen isolated cases of Best's disease. Vision in this affection is frequently good, sometimes even 5/5, as the lesion is generally situated below the macula. In one case there was colour blindness which was almost complete. Best believed that two of his eight cases showed the lesion on one side only, but in a subsequent study Jung doubts these two cases, as the ophthalmoscopic changes fell within normal limits. Vossius holds that the lesion is not always congenital, but the evidence for this too is not found convincing by Jung. There is, however, no conclusive evidence that the affection is indeed congenital; it has not been observed as such and the assumption that it is congenital is based upon its non-progressive character and upon the personal histories which go back to childhood—in such of the cases in whom vision is poor.

(iii) *Macular dystrophy.*

In contrast to the two previous affections with their gross ophthalmoscopic lesions and their congenital or early onset, the macular dystrophies may show but mild disturbances ophthalmoscopically and develop in patients who previously had good vision. Behr's classification (1920) of the macular dystrophies has the merit of emphasising their abiotrophic character, for in addition to the group of probably congenital lesions described by Best and the cases developing in childhood as noted by Stargardt and other observers, Behr drew attention to cases developing in early adult life, at the beginning of involution (" pre-senile," at 45 years) and further argued that some cases of senile macular degeneration may be familial and represent the end of a series beginning with a congenital lesion and running through different forms making their appearance at the critical ages: at the second dentition (6-8 years), at puberty, at full adult life (20 years), at the presenium (45 years) and in senility. Behr could not advance any proof that familial cases do occur in senility, but this is now available in the families reported by Waardenburg (1936 and 1938).

Morphologically Behr admitted macular lesions ranging from mild changes to central disturbances generally covering an area of ½-1 D.D., though in one case an area 5 D.D. was involved. He emphasised the purely macular character of the lesion and held that any optic nerve involvement that may occur in these cases is an associated lesion and not part of the picture. None the less extension beyond the macular area is not uncommon and peripheral lesions have been reported.

Ophthalmoscopically the appearances seen in macular dystrophy show a wide range, the usual variants being fine pigmentary mottling which is easily missed, whitish dots with but little pigment disturbance, and atrophic areas. Central pigmentary changes of the retinitis pigmentosa type have been reported, and also appearances suggestive of retinitis punctata albescens.

In discussing the functional disturbances seen in macular dystrophy, Behr pointed out the frequent occurrence of colour anomalies and even total colour blindness. In cases of total colour blindness the macular lesion is generally not marked, but the existence of such lesions lends further support to the view that there is no sharp demarcation between the congenital type of macular lesion and the macular dystrophy of later onset.

(iv) *Doyne's choroiditis.*

The literature on this affection is sparse. Doyne drew his material from two families, recently more fully described by Tree (1937). Isolated cases have been reported by Holthouse and Batten (1897), Bickerton (1900), Morelli (1928) and more recently by Malbran and Adrogue (1936) and Tanaka (1938). Foster (1932) described two brothers as doubtfully belonging to this group; these cases are more fully discussed below (K. family, p. 481). The affection is said to develop at about 40 years of age and is characterised by massive formation of white dots in the disc-macular area; pigmentation is slight and atrophic areas ultimately form. Haemorrhages may be present during the course of the affection, and occasionally, also, a honeycomb pattern.

(v) *Angeoid streaks.*

This too must now be regarded as a familial affection confined essentially to the central and paracentral areas. The recognition of the associated pseudoxanthoma elasticum (Grönblad, 1929) and of elastic tissue degeneration in the big systemic vessels (Böck, 1938; Prick, 1938) puts this affection in a category of its own: elastosis dystrophica, the ocular lesion being caused by degenerative changes (ruptures) of the elastic membrane of Bruch.

(vi) *Central choroidal sclerosis.*

The familial occurrence of central choroidal sclerosis has been the subject of a recent study (Sorsby, 1939). Here it is only necessary to emphasise that the early stages may simulate a retinal macular dystrophy.

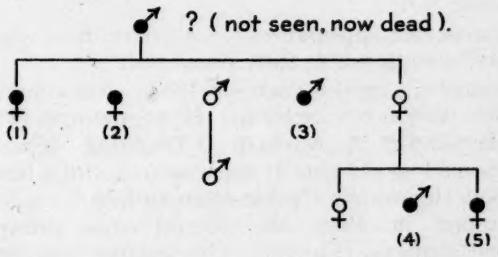
It is obvious that of these six forms of familial affections of the central area of the fundus, congenital macular coloboma, angeoid streaks and central choroidal sclerosis are clear-cut clinical groups, but in the three remaining affections the line of demarcation is

faint. The problem they raise is to what extent do these three forms—Best's disease, Doyne's choroiditis and the macular dystrophies with their considerable range of clinical appearances —represent different aspects of fundamentally the same retinal dystrophy, which in different families shows a different ophthalmoscopic appearance, and has a different clinical course and genetic behaviour. That extensive variations may occur within the same affection is well known from the behaviour of retinitis pigmentosa with its recessive and dominant forms, its early or late onset, and its mild or severe course in different families.

(2) Personal Observation

(i) *The C. Family.*

Family history.—Father had bad sight all his life; mother was normal. No consanguinity. Of the three daughters, two are affected, as is also one of the two brothers. The unaffected brother has a normal child, and the affected sisters are unmarried. The unaffected sister has three children, two of whom are affected.* The affected brother has no children.



(1) *Edith C.*, aged 43 years, when first seen in 1933. Vision defective since childhood, and continued steadily worse till about the age of 30 years. Lately she has experienced special difficulty at night. Vision: R: and L: > 6/60. Colour sense (Ishihara test): normal. Fields: full. No central scotoma. Emmetropic.

Ophthalmoscopic appearances (1933): Figures 1 and 2.

The macula and an area 3 D.D. shows extensive mottling with white and pigmented dots. The rest of the fundus is normal, and though the choroidal pattern is clearly seen, there is no suggestion of retinal atrophy peripherally. The appearances in the two eyes

* These children and their aunts were demonstrated before the Royal Society of Medicine in 1934. (*Proc. Roy. Soc. Med.*, Vol. XXVII, p. 694, 1934).

are similar except that in the right eye the choroidal vessels are exposed in the macular area and in the left eye no such vessels are seen in this region.

Re-examined in 1938, the appearances were essentially unchanged. There was no indication of any choroidal sclerosis.

(2) *Harriet C.*, aged 39 years (in 1933). The history and subjective findings are as for her older sister. Like her sister, she is emmetropic, is certified blind and works in a blind factory.

Ophthalmoscopic appearances (1933): Figures 3 and 4.

These are similar to those seen in the older sister, but the lesion is more advanced and rather more irregularly distributed. In the right eye the choroidal vessels are clearly seen in the macular area in which the pigment changes are tending to assume a more conglomerate distribution. In the left eye the appearances are not so fully developed and are intermediate between those seen in the right eye and the changes shown by the elder sister. There is no definite involvement of the retina beyond the central area.

Re-examined in 1938, the condition was essentially unchanged and like in the elder sister there was no evidence of any central choroidal sclerosis.

(3) *John C.*, aged 34 years. Vision: > 6/60 in each eye. No obvious difficulty at night. Is doing sighted work. Seen on one occasion only.

Ophthalmoscopic appearances: Similar to those shown by the elder sisters, though not so fully developed.

(4) *Bernard C.*, aged 8 years (in 1933). Not conscious of any eye trouble. Vision 6/6 each eye. Hypermetropia (2·0 D.).

Ophthalmoscopic appearances: Doubtful departure from normal. Some loss of lustre at macular area with a few ill-defined whitish spots suggesting a worm-eaten surface.

Re-examined in 1938, the central area showed definite pathological changes. (Fig. 5.) The macular area itself showed several patches of gross pigment lying on an atrophic background. Surrounding these central changes were a number of white dots. The appearances in the two eyes were similar. Vision is now 6/9. Not conscious of any visual defect.

(5) *Betty C.*, aged 5 years (in 1933). Not conscious of any eye trouble. Vision 6/6 each eye. Hypermetropia (2·50 D.).

Ophthalmoscopic appearances in 1933 as in her brother, but less marked.

Re-examined in 1938 the macular lesion was well established (Fig. 6). It consisted of some heightened pigmentation over the central area without the gross pigmentary changes seen in her brother. In addition there were whitish dots surrounding this zone, not extending so diffusely as in the boy.

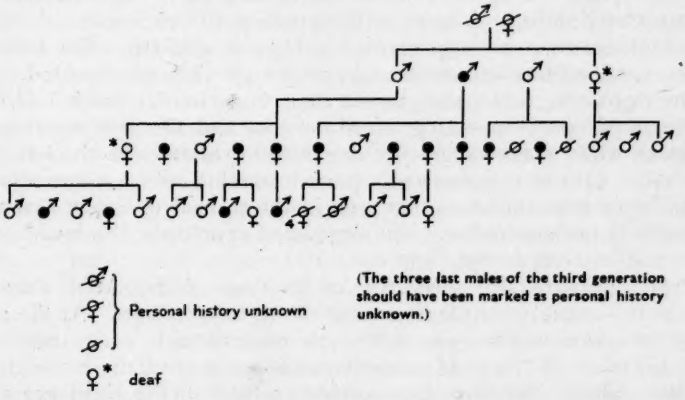
Remarks.—This group has the following points of interest:

(1) Unusual mode of inheritance, probably irregular dominance.
(2) Early onset of ophthalmoscopic changes in the children.
(3) The extensive ophthalmoscopic changes seen in the end stage in the two aunts, emphasising the fact that macular dystrophies need not remain confined to the central area.
(4) The onset of some night-blindness with the progress of the affection in the aunts.
(5) Judging by the slow decline in central visual acuity in the children, the lesion is not rapidly progressive.

(ii) *The M. Family.*

Family history.—Mrs. M. (1) is the mother of John M. (2) and the maternal aunt of Bernard W.* (3). The mother of Bernard W. is said to have poor vision since childhood.

The family is extensive and the following tree, prepared by Bernard W. who is a male nurse, indicates the large number of members that are said to be affected.


Personal history unknown
(The three last males of the third generation should have been marked as personal history unknown.)
deaf

If this tree is accepted on its face value, a doubtfully affected great-grandmother, transmitted the affection to one son and four of his daughters. Nothing is known of the children of one of the affected daughters, whilst the children of two other affected daughters are normal. Of the three unaffected members of the

* B.W. was demonstrated by Frederick Ridley before the Royal Society of Medicine in 1937. (*Proc. Roy. Soc. Med.*, Vol. XXX, p. 390, 1937).

second generation, the condition of the daughter's children is unknown, whilst her two (normal) brothers had affected daughters. In the fourth generation there are affected sons and daughters of an unaffected mother, and affected sons of affected mothers.

(1) *Mrs. M.*, aged 39 years. Trouble began at about the age of 20 years. Vision with correction: R: 6/24, L: 6/60. Patient was not seriously handicapped till after the birth of her only child (described below) eleven years ago. Vision has become worse recently with the onset of pregnancy; an affected sister who had two children (one being B.W. described below) is said to have experienced a similar deterioration of vision with each pregnancy. Hysterectomy was performed on the patient and there appeared to be some improvement in vision.

Ophthalmoscopic appearances: (Figs. 7 and 8). The lesions are more marked in the right eye than in the left. In both central areas there are whitish masses suggestive of exudate. They appear to be slightly raised on the surface and some of the patches are of a whiter and harder colour than others. The lesion in the right eye is bordered below by a sharply marked white streak with some pigmentary changes. The lesions appeared more quiescent after the termination of the pregnancy.

(2) *John M.*, aged 11 years (son of Mrs. M.). Is not aware of any visual defect. Vision with correction 6/9 each eye.

Ophthalmoscopic appearances: (Figs. 9 and 10). The lesions are confined to the central areas which are diffusely mottled. In the right eye, below the macula there is a circular patch 1 D.D., the upper part consisting of white dots and the rest showing a dense white mass suggesting organized exudate. In the left eye a more or less symmetrically placed circular area has essentially the same appearance as that seen in the right eye, except that the patch is more atrophic. The organized exudate at the lower pole is smaller than in the right eye.

(3) *Bernard W.*, aged 26 years (nephew of Mrs. M.). Patient was not aware of any eye trouble till 18 months ago. At the age of 24 years vision was 6/6 each eye, though even then the appearance of " a hole at the macula " was present in the right eye. Vision has since deteriorated to 6/60 in the right eye and 6/9 in the left. His mother, who apparently is likewise affected, had vision of 6/18 in each eye at the age of 52 years.

Ophthalmoscopic appearances: (Figs. 11 and 12). The left eye shows the same generalized mottling of the central area that is seen in John M. The right eye shows in addition an appearance suggestive of a hole at the macula. In contrast to the lesions seen in Mrs. M. and her son, there is nothing to suggest an exudative reaction in this patient.

Remarks:—

(1) The ophthalmoscopic changes are unusual. Seen by themselves as isolated patients, Mrs. M. and her son would suggest, because of the exudative reaction, a diagnosis of either central choroiditis or of a central retinitis of an obscure type.
(2) The more classical changes shown by B.W. emphasize the considerable variation possible within the same family.
(3) There is preservation of fair vision in spite of extensive ophthalmoscopic changes.
(4) The mode of inheritance is probably irregular dominance.
(5) The severe ophthalmoscopic lesion without serious visual disturbance in the boy at 11 years of age cannot be regarded as evidence of a possibly mild course in view of the deterioration in sight observed in his uncle during the last eighteen months.

(iii) *The N. Family.**

Family history.—Parents are first cousins. They have normal vision. Father practically emmetropic: mother hypermetropic (+ 4·50 D. sph. + 0·5 D. cyl.).

Evelyn Mary N.: First seen at 12 years of age (in 1915). Vision said to have failed a few days before. Vision with correction (high hypermetropia) R: 6/12, L: 6/18. Nothing abnormal seen in fundus. Two years later "changes at both yellow spots." Drawings (Figs. 13 and 14) were made in 1928 at age of 25 years, *i.e.*, 9 years after changes first observed at maculae. The lesion in the right eye had become more pigmented, and was a little flatter, it having been definitely raised when first noted. The appearances in the left eye had not changed appreciably. Last seen in June, 1938, when vision in the right eye, which has steadily deteriorated, was 6/60 and in the left 6/18 (with correction, R: + 5·0 D. sph. ⊂ - 2·75 D. cyl., L: + 7·0 D. sph. ⊂ - 3·0 D. cyl.). The central area over a large extent is becoming atrophic; the left eye showed no obvious changes.

Kingsley N.:—First seen in 1914 at the age of 8. Vision with correction (+ 4·50 sph. ⊂ 1·5 D. cyl.) was 6/18 in each eye. Round masses of exudate, mostly white in colour, were present at both maculae. In 1920 there was no change, apart from slight flattening of the exudate. In 1928—when the drawings (Figs. 15 and 16) were made—vision in each eye was 6/12, and the fundi showed a circular greyish area in the region of the old patches

* Not seen personally. Patients of Mr. Harold Grimsdale, to whom I am obliged for the clinical details.

of white exudate. Last seen in November, 1934, at the age of 28 years, when vision was R: 6/12, L: 6/9, binocularly 6/6 partly. The appearances had not changed substantially.

Two more members of this family have been examined. A brother now aged 35 is normal; vision with + 1·50 D. sph. is 6/4p. each eye. A brother of the father who had full vision with correction but showed (in 1913) a small whitish patch below the left disc " sharp and hard, ? retinal exudate."

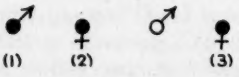
Remarks:—

(1) The ophthalmoscopic appearances in these two patients lend support to the existence of an " exudative " type of macular dystrophy illustrated by the M. family.

(2) The preservation of good vision in one of the patients over a period of 20 years (between the ages of 8 and 28) is as noteworthy as the decline in visual acuity in his sister.

(iv) *The A. Family.*

Family history.—Mother married twice. No consanguinity in either marriage. There are three children from the second marriage, a twin boy and girl aged 4 years and a boy aged 6 months: they are normal. The affected children—3 out of a sibship of 4—come from the first marriage. Their father is dead; his sight is said to have been good.



(1) *Henry John A.*: Aged 17 years. Vision bad throughout school life. He had to attend at a school for partially-sighted children. Not getting worse. No night-blindness. Vision is less than 6/60 in each eye. Emmetropic. Heavy colour defect; in the Ishihara test misses all figures except those for red-green vision, on which he is uncertain. Fields full. No central scotoma.

Ophthalmoscopically (Fig. 17) there is an atrophic area at the macula about 1½ D.D., bordered by finely scattered pigment. The fundus immediately surrounding the area of the disc—macula region is normal, but towards the equator there are gross pigmented and atrophic areas, not suggestive of retinitis pigmentosa extending towards the periphery in a progressively diminishing manner. The disc and vessels are normal. The two eyes are fairly equally involved.

(2) *Florence A.*, aged 15 years. Like her brother she attended a school for partially sighted children. Not conscious of any

deterioration in vision. No night blindness. Vision: R and L: 6/60. Emmetropic. Colour sense (Ishihara test): normal. Field full. No central scotoma.

Ophthalmoscopically (Fig. 18), in each eye the macular area over 1 D.D. is atrophic with fine pigment disturbances. This is the most striking lesion, but scattered over the greater part of the fundus, more especially towards the periphery are numerous fine white and pigmented dots, some of them ghost-like in appearance. The disc is normal, but the vessels are rather narrow.

(3) *Kathleen A.*, aged 9 years, is the fourth member of the family. Her immediate senior, a boy aged 13 years, is normal. She herself has never seen well at school and is now attending a school for partially-sighted children. No night blindness. Vision: R: > 6/60, L: 6/60. Emmetropic. Colour sense (Ishihara test): normal. Field full. No central scotoma. Faint lamellar opacities are present in both lenses.

Ophthalmoscopically (Fig. 19), the macular area over 1 D.D. shows fine pigmentary changes of a pathological character. The immediately surrounding zone is normal. Beyond this the whole fundus shows fine mottling, and towards the equatorial region pigmentary changes strongly reminiscent of the " bone-corpuscle pigment " are present, some arranged along the vessels. The disc and vessels are normal.

All the three children are emmetropic.

Remarks:—

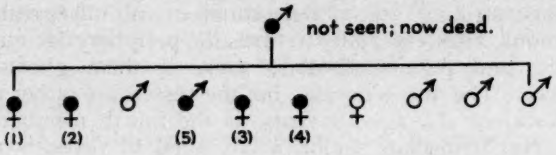
(1) In addition to the macular lesion with gross disturbance in the acuity of central vision, this group illustrates (*a*) peripheral involvement of the fundi and (*b*) appearances suggestive of retinitis pigmentosa as shown by the state of the arteries in the second child and the pigment changes in the youngest. The absence of night-blindness is noteworthy.

(2) The fundus appearances approach those seen in cerebro-macular degeneration, but there are no neurological or psychic changes in this group.

(v) *The K—r Family.*

Family history.—Father died 20 years ago practically blind at the age of 63 years. The eye trouble began at about the age of 40 years. He was one of a large family and " nearly all his brothers were affected." The son of one of the brothers is also said to be affected. There was no consanguinity between the father and mother. There were 10 children, 5 sons and 5 daughters. Four of the daughters were personally examined and

are affected. The fifth daughter is said to be normal. Of the 5 sons nothing is definitely known of the eldest and another appears to be affected. The 3 remaining sons are the youngest members of the family, being 45, 44 and 42 years of age respectively.



(1) *Mrs. A. H.*, aged 62 years. Vision 1/60 in each eye. Sight began to fail about 20 years ago, but does not seem to have deteriorated lately. She has one daughter, aged 21 years, who is said to be normal.

Ophthalmoscopic appearances: (Figs. 20 and 21). There is some mild retinal arteriosclerosis, but the most striking lesion is an extensive area of retinal atrophy situated centrally in both eyes with massive pigmentary changes in the more central part of this atrophic area. There is some evidence of choroidal sclerosis deep to the pigmented patches. Towards the periphery there are a number of white dots situated deep to the retinal vessels.

(2) *Mrs. W. P.*, aged 60 years. Vision 1/60 in each eye. Sight had been failing for 20 years and became markedly worse after the birth of her third child. There are three daughters aged 24, 22 and 19 years respectively. They are said to be normal.

Ophthalmoscopic appearances: (Figs. 22 and 23). The lesion is similar to that in her elder sister, but is more strictly confined to the maculae. The peripheral white dots are far fewer. Some of the pigment is clustered around the vessels, but does not suggest the bone corpuscle pigment of retinitis pigmentosa; the arteries are normal. Here and there " exudates " are present.

(3) *Mrs. A. R.*, aged 53 years. Vision 6/60 in each eye. The trouble began about the age of 40 years and has steadily got worse. There are three daughters and two sons; all are said to be normal.

Ophthalmoscopic appearances: (Figs. 24 and 25). These bear little resemblance to those seen in her sisters. There is an extensive area of peripapillary retinal atrophy with comparatively little pigment disturbance. Towards the periphery there is some suggestion of choroidal sclerosis. The central areas themselves are not heavily involved.

(4) *Mrs. R. G.*, aged 50 years. Vision 3/60 in each eye. The right eye failed 4 years ago and the left 18 months ago. One of

her two daughters is mentally defective; her only son aged 12 years was examined and found normal.

Ophthalmoscopic appearances: (Figs. 26 and 27). There is a diffuse retinal atrophy as shown by appearances suggestive of "pepper and salt," but the most striking feature is the heavy central pigmented lesion with outlying dirty gray dots most marked in the right eye. There is a small haemorrhage a little below the disc at 7 o'clock in the right eye and there is some suggestion of an exudative reaction. Considerable retinal atrophy is further suggested by the map-like contours seen in the left central region.

(5) *W. K.*, aged 55 years. This patient could not be examined but there is a history of his having attended Moorfields Eye Hospital at the age of 47 years when the condition was diagnosed as slight choroiditis right eye and macular choroiditis left eye.

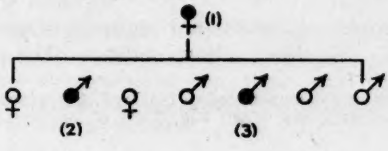
None of the four sisters examined showed any obvious contraction of the peripheral field. On Stilling tables they were heavily colour defective. None appeared to have night-blindness.

Remarks:—

(1) In spite of the appearances in Mrs. A. R. it must be assumed that the lesion in this family is primarily macular, though there is considerable peripheral extension.
(2) The striking feature in this group is the heavy central pigmentation. In two members of the family there is some "exudative" reaction.
(3) The pigmentation does not appear to bear any relationship to retinitis pigmentosa, but is much more suggestive, if seen in an individual case, of an inflammatory lesion of the choroid.
(4) The late onset in this family (after the age of 40 years) is noteworthy.
(5) The history indicates dominant inheritance.

(vi) *The K. Family.*

Family history.—Parents not consanguineous. Father's vision R: 6/6, L: 6/60. (Right eye emmetropic; left high myopia). Mother illiterate, not conscious of any eye trouble—but fundi show pathological changes. There are seven children: five



brothers and two sisters. Two of the brothers are affected;* the other sibs are normal. The family is Jewish.

(1) *Mrs. K.*:—The central areas of the fundus show ill-defined whitish dots. These are more obvious towards the periphery. They do not constitute a marked lesion, but they cannot be regarded as normal. There is no retinal arterio-sclerosis.

(2) *Harry K.*, aged 37 years. Patient was not aware of any eye trouble until the age of 28 years. He went through his school career without any difficulty. There is no night-blindness and no colour defect. No central scotoma. Peripheral fields full. In February, 1931, vision was R: 6/24, L: 6/18. This had declined by one line within four months and deterioration has continued. Vision is now less than 6/60 each eye.

Ophthalmoscopic appearances: (Fig. 28). The discs and vessels are normal. A number of fine white dots are scattered over the fundi, lying on a more superficial plane than a diffuse grayish mottling of a rather gross character which is present over the greater part of the fundus, but most marked in the central areas, where slight pigmentary disturbances are seen in addition.

(3) *Mark K.*, aged 31 years. The patient first noticed eye trouble at about the age of 20 years. In 1931 his vision was R: 6/24, L: 6/12, which has deteriorated progressively and is now less than 6/60 each eye. The subjective findings are like those in his brother.

Ophthalmoscopic appearances: (Fig. 29). These are similar to those seen in his brother, except that the superficial whitish dots are not present and the grayish areas scattered over the fundi, but most marked centrally, are more defined giving a definite pattern. Some of these patterned figures show pigmentation. At the macula itself a number of white dots form a clear pattern.

Remarks:—

(1) The patterned appearance in the two brothers in 1931 suggested the diagnosis of Doyne's choroiditis. The pattern has become less obvious with time, being lost in a more diffuse central degeneration.

(2) The ill-defined changes in the mother suggest a dominant transmission, and perhaps also anticipation and a more severe course in her affected sons.

(vii) *The B. Family.*

Family history.—Parents not consanguineous. There were nine children. The third, a boy, is dead. The patient, the eldest

* These patients were demonstrated in 1931 by J. Foster before the Royal Society of Medicine (*Proc. Roy. Soc. Med.*, Vol. XXV, p. 90, 1932) as cases of ? Doyne's choroiditis.

in the family, is the only one who has visual trouble, but two other members of the family show fundus lesions.

(1) *Mrs. Marie B.*, aged 34 years when seen in 1934. Vision with glasses (low myopia) 6/60 each eye. Trouble dates back to the age of 17 years. There is no night-blindness. Fields full. With the Ishihara test there is gross colour anomaly, the patient being best on red and green. The patient has four children, three boys and a girl. Their fundi are normal.

Ophthalmoscopic appearances: In 1934 the central areas of both fundi showed numerous white dots of a gross type, diagnosed as colloid degeneration. Vision has not deteriorated further, but the ophthalmoscopic appearances have changed considerably. The pattern originally present has disappeared and the fundi show a metallic lustre in the central areas with considerable pigmentary changes (Figs. 30 and 31).

(2), (3), and (4). A sister and brother, the fourth and fifth members of the family, show white dots of the colloid type in the central areas of the fundi extending up to the equator. Their vision is full. The youngest member of the family is normal. The others have not been seen.

Remarks:—

(1) The pattern, originally seen in Mrs. B. and now lost, as also the appearance of colloid bodies in a brother and sister, suggested the possibility of Doyne's choroiditis as a diagnosis.

(2) The subsequent course involving the loss of a pattern illustrates the unreliability of the appearance in an intermediate stage as a criterion for diagnosis.

(viii) *The F. Family.*

Family history.—Parents normal. No consanguinity. There are eighteen children. Two daughters are affected,* the fourteenth and fifteenth in the family.

(1) *Helen F.*, aged 27 years when first seen in 1932. Vision was C.F. each eye. There is marked keratoconus, blepharospasm

* These cases were mentioned, but not described in an earlier paper. (*Trans. Ophthal. Soc. U.K.*, Vol. LIV, p. 166, 1934).

and nystagmus. On the Ishihara test she is totally colour blind. She sees rather better in the dusk than in broad daylight.

Ophthalmoscopic appearances: There is fine mottling of a pathological character at the right macula. The fundus details of the left eye could not be clearly seen.

(2) *Rosina F.*, aged 29 years in 1932. Vision and the subjective symptoms are the same as in her sister, but there is no keratoconus.

Ophthalmoscopic appearances: The left macula shows an atrophic area. The right fundus could not be seen clearly, but there were a number of white spots scattered over the fundus.

Remarks:—

(1) The fundus lesion is presumably congenital, as are the other symptoms.
(2) As in most cases of total colour blindness with macular lesions, the ophthalmoscopic appearances are not marked.

Summary.

This group of eight families illustrates not only the extensive range of ophthalmoscopic appearances in macular dystrophy, but also the lack of uniformity as regards genetic behaviour, age of onset, course and effect on vision. As far as ophthalmoscopic appearances are concerned the children in the first group (family C.) illustrate the classical type of macular dystrophy, but the end stage seen in their aunts shows that the lesion can hardly be regarded as purely macular. The M. and N. families bring out a type not noted before, in as much as an " exudative " reaction has not been regarded as a manifestation of macular dystrophy. The A. family adds to a type which has obtained some recognition, for the literature records cases of " inverse retinitis pigmentosa," whilst the K—r family showing massive central pigmentary disturbances has an interest as a possible connecting link between the classical type and this " inverse retinitis pigmentosa " type and possibly also the " exudative " type. The K. family and the B. family illustrate the fine line of demarcation between Doyne's choroiditis and the macular dystrophies and in view of the present report of two familial groups showing an " exudative reaction," the line becomes finer still, and Doyne's choroiditis must be regarded as nothing more than a variant of macular dystrophy, showing a pattern of " exudates " at one stage in the course of its development. The F. family is yet a further illustration of the wide range of macular lesions seen in total colour blindness.

KEY TO ILLUSTRATIONS

Figs. 1-36 refer to case reports in the present paper:—

Figs. 1-6 concern the C. family; Figs. 7-12 the M. family; Figs. 13-16 the N. family; Figs. 17-19 the A. family; Figs. 20-27 the K—r family; Figs. 28-29 the K. family; Figs. 30-31 the B. family; Figs. 32-33 the F. family; and Figs. 32-36 illustrate three isolated cases. (For a summarised description of the reactions shown by these cases see p. 484).

Figs. 37-56 are illustrations taken from the literature to show different types of ophthalmoscopically observed reactions.

Figs. 37-41: Various appearances in which the lesion consists essentially of mottling of the central area.

Figs. 42-46: Various appearances of established atrophy at the macula.

Figs. 47-51: Unusual variants. Inverse retinitis pigmentosa, Doyne's choroiditis, rosette figure, and extensive peri-macular involvement.

Figs. 52-56: The great range of ophthalmoscopic variants seen within several separate families.

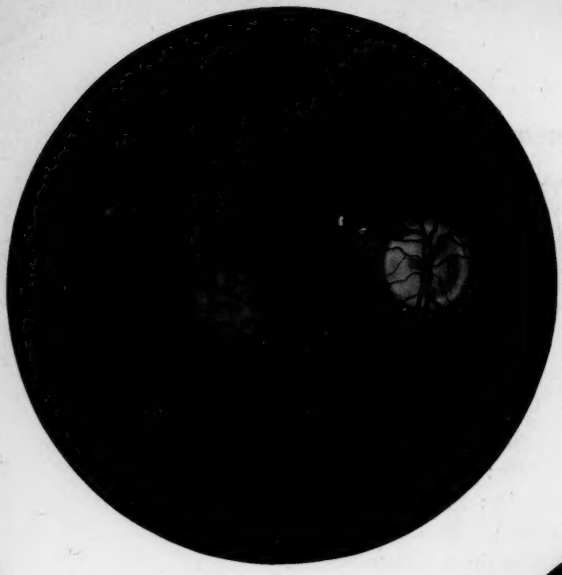


FIG. 1.

The macula and an area 3 D.D. show extensive mottling with white and pigmented dots. The choroidal vessels are exposed. The rest of the fundus is normal and though the choroidal pattern is clearly seen, there is no suggestion of retinal atrophy peripherally.

Fig. 2 shows somewhat milder changes in the left eye. These drawings were made when the patient was 43 years old.

Figs. 3 and 4 show essentially similar changes in the patient's sister, aged 39 years, whilst Figs. 5 and 6 show the early stages seen in a nephew and niece aged 13 and 10 years respectively.

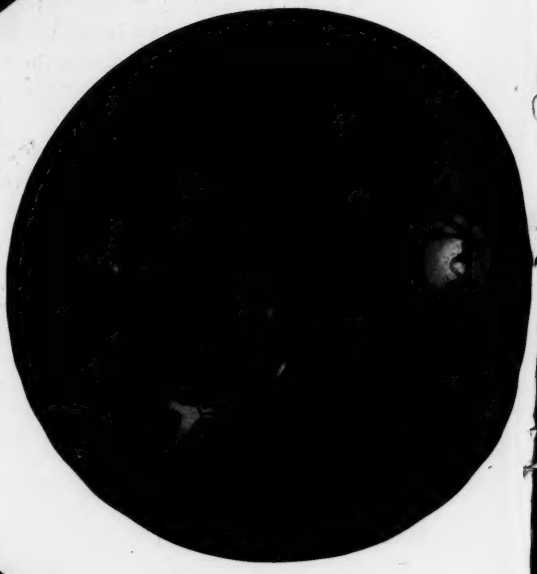


FIG. 7.

In the central area there are whitish masses suggestive of exudate. They are slightly raised and some of the patches are of a harder colour than others. The lesion is bordered below by a sharply marked white streak with some pigmentary changes.

Fig. 8 shows the somewhat milder changes in the left eye. These drawings were made when the patient was 39 years old.

Figs. 9 and 10 show the appearances in the patient's son aged 11 years.

Figs 11 and 12 show the changes seen in the patient's nephew aged 26 years.

These three patients illustrate a wide range of lesions extending from fine mottling, to hole formation and "exudative" reaction.

Figs. 13 to 16 show the changes seen in a brother and sister of an unrelated family, and are further examples of the "exudative" reaction.

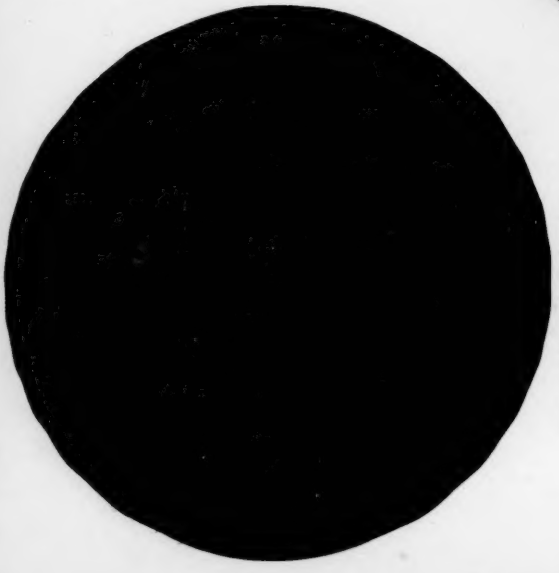


FIG. 19.

There is fine pigmentary mottling at the macula, and some mottling peripherally beyond a normal zone surrounding the central lesions. Characteristic "bone-corpuscle" pigment is present, but the disc, arteries and veins are normal. Vision is 6/60; there is no night-blindness. The patient is aged 9 years.

Fig. 18 shows the changes seen in a sister aged 15 years, who shows a mottled, atrophic macula and peripheral pigment changes not suggestive of retinitis pigmentosa. The arteries are narrow.

Fig. 17 shows an advanced macular lesion with gross peripheral pigment changes in the brother aged 17 years.

FIG. 2. For legend see Fig. 1.

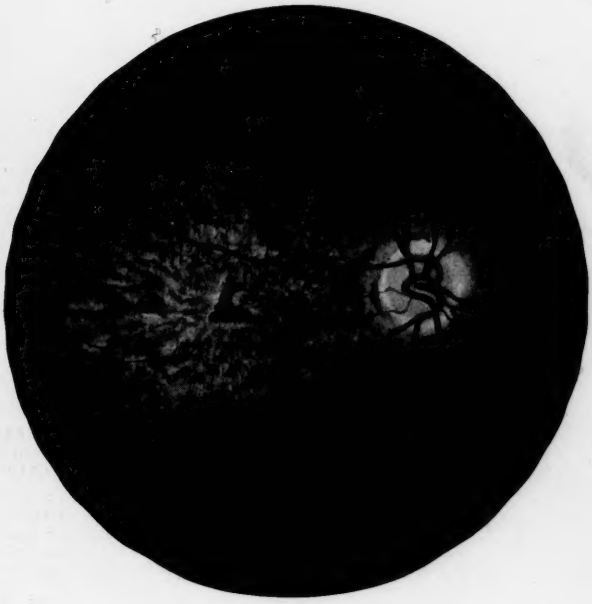


FIG. 3. For legend see Fig. 1.

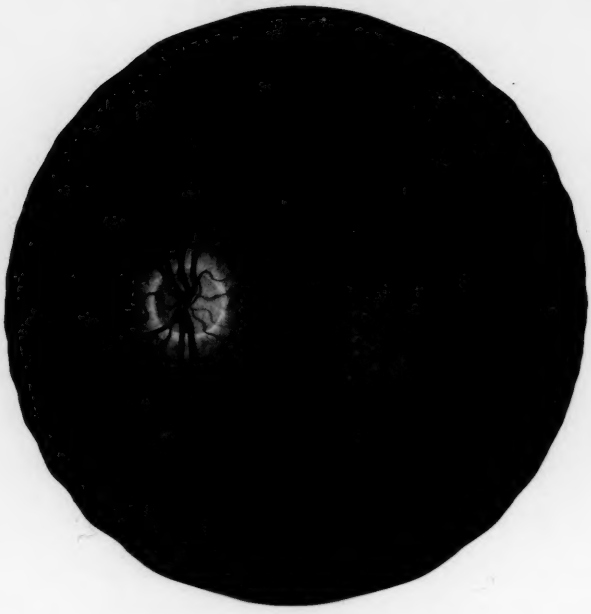


FIG. 4. For legend see Fig. 1.

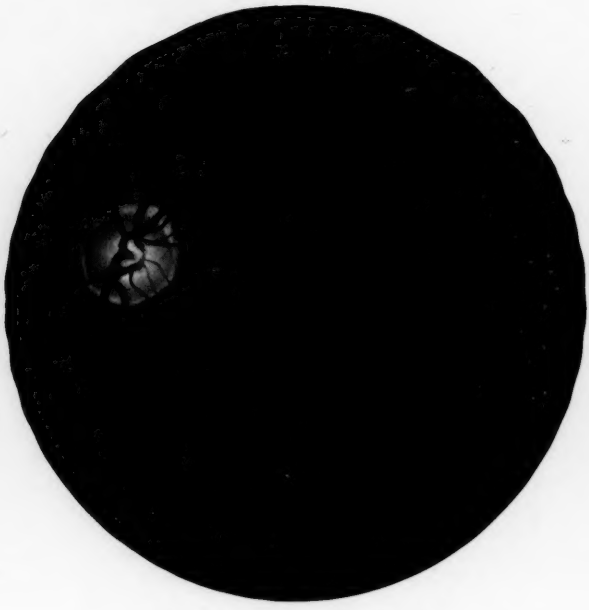


FIG. 5. For legend see Fig. 1.

FIG. 6. For legend see Fig. 1.

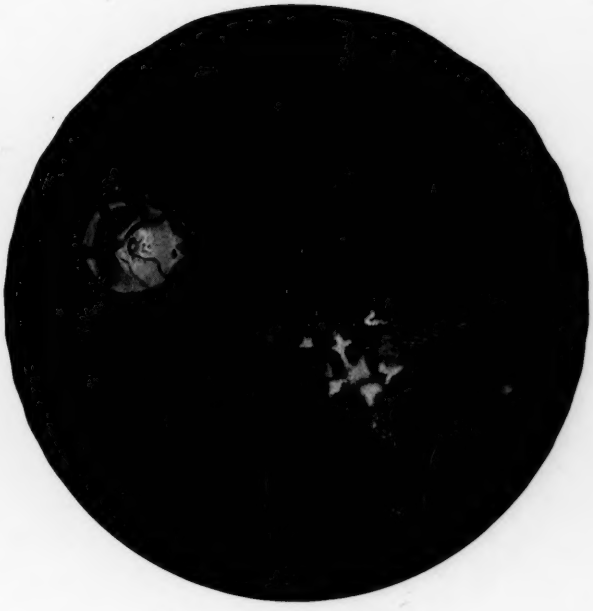


FIG. 8. For legend see Fig. 7.

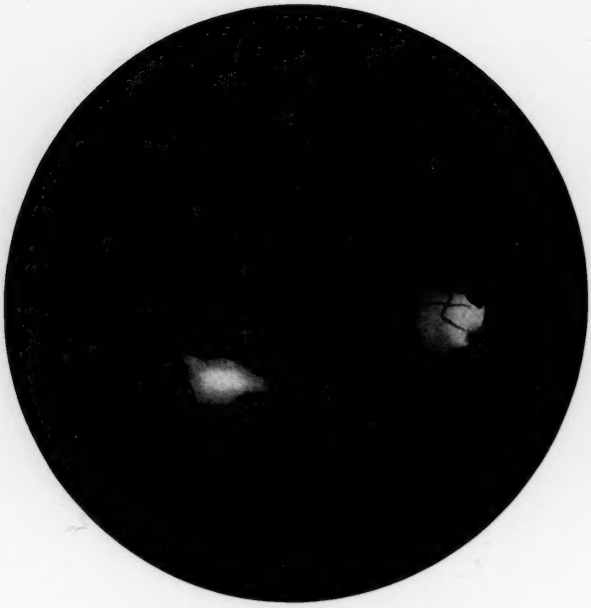


FIG. 9. For legend see Fig. 7.

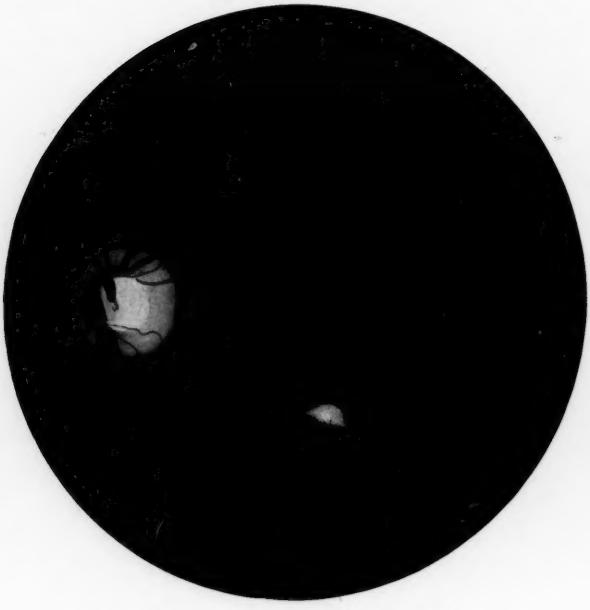


FIG. 10. For legend see Fig. 7.

FIG. 11. For legend see Fig. 7.

FIG. 12. For legend see Fig. 7.

FIG. 13. For legend see Fig. 7.

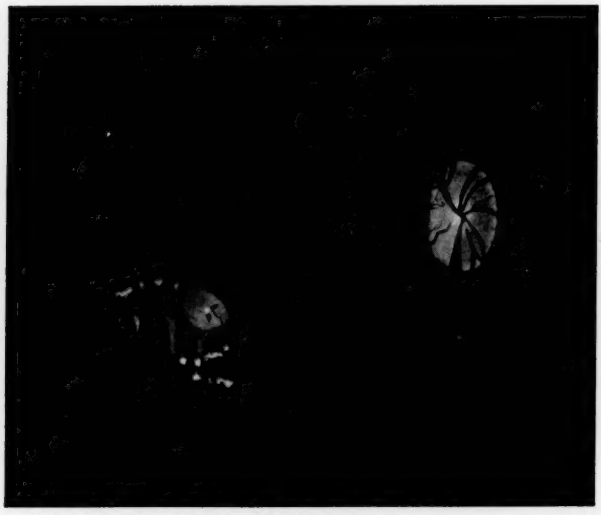


FIG. 14. For legend see Fig. 7.

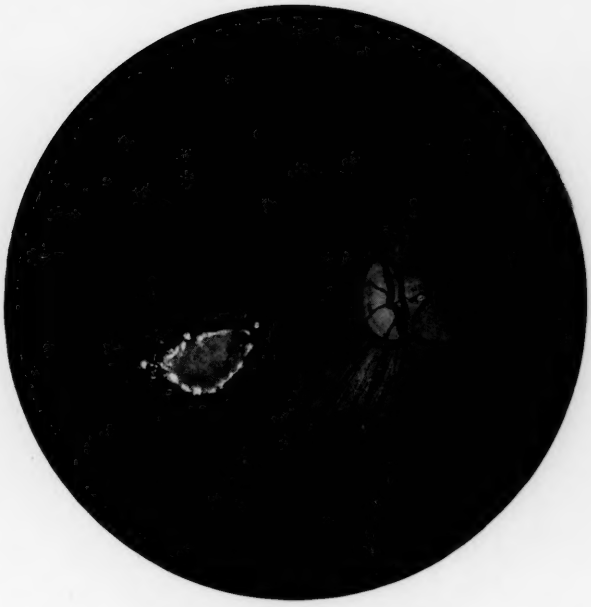


FIG. 15. For legend see Fig. 7.

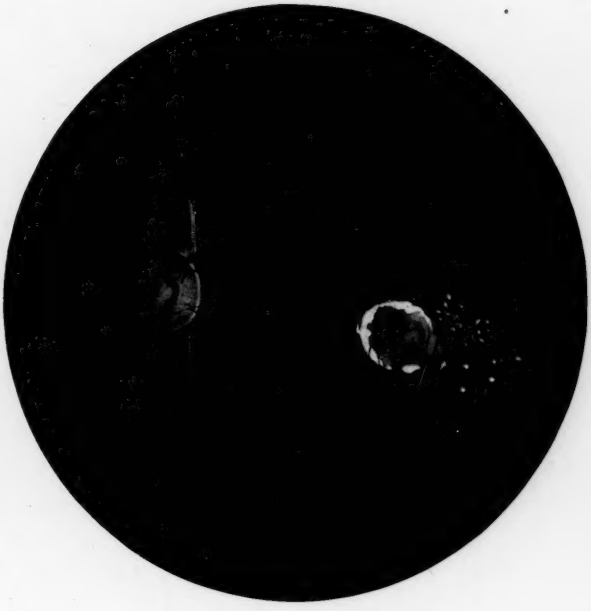


FIG. 16. For legend see Fig. 7.

FIG. 17. For legend see Fig. 19.

FIG. 18. For legend see Fig. 19.

FIG. 20. For legend see Fig. 26.

FIG. 21. For legend see Fig. 26.

FIG. 22. For legend see Fig. 26.

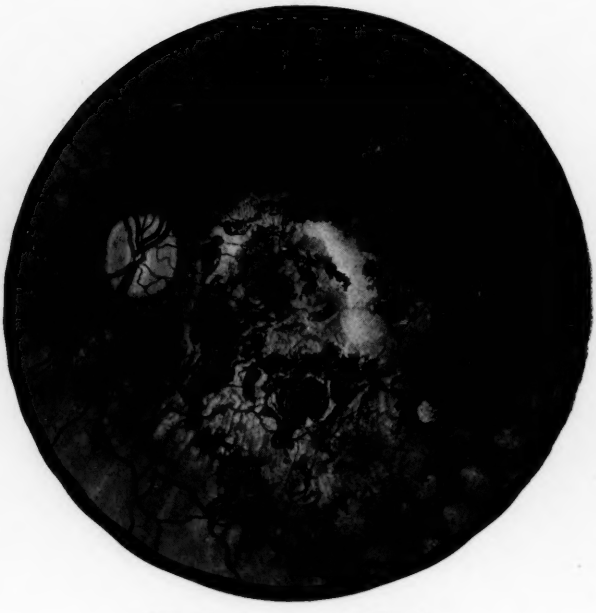


FIG. 23. For legend see Fig. 26.

FIG. 24. For legend see Fig. 26.

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FIG. 27. For legend see Fig. 26.

FIG. 28. For legend see Fig. 29.

FIG. 30. For legend see Fig. 29.

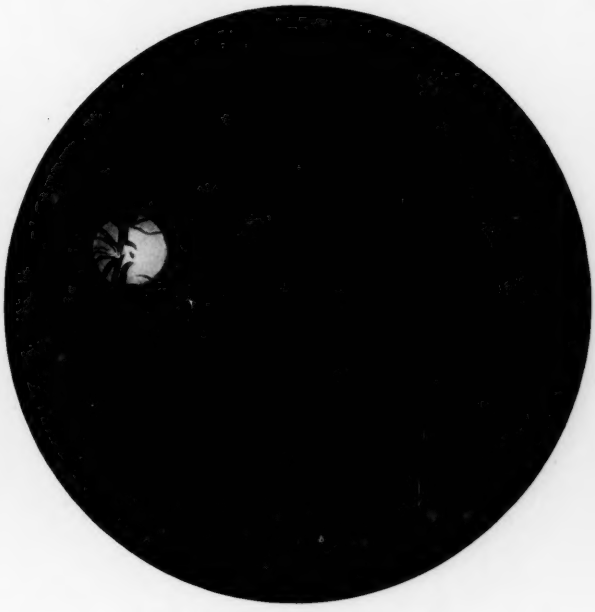

FIG. 31. For legend see Fig. 29.

FIG. 32. For legend see Fig. 29.

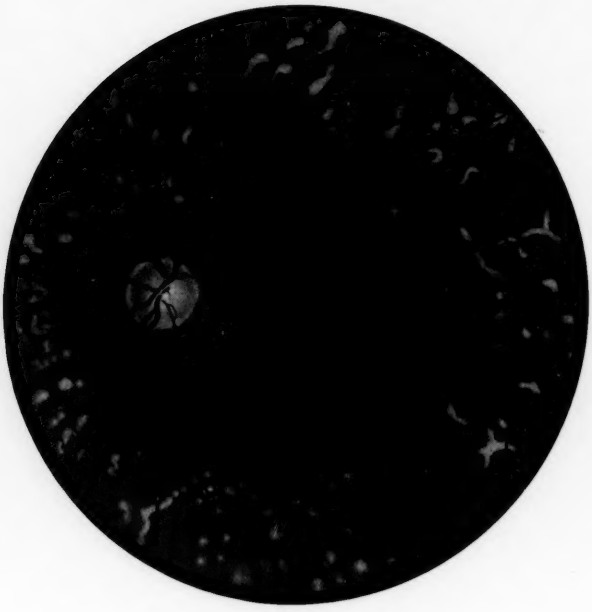

FIG. 33. For legend see Fig. 29

FIG. 34. For legend see Fig. 35.

FIG. 36

The right fundus of a patient of consanguineous origin. Essentially similar changes were present in the left eye. In additon to the macular lesion there is widespread retinal atrophy and incipient choroidal sclerosis. No other member of the family appears to be affected.

FIG. 26.

There is heavy pigmentary disturbance in the central region over an area of more than 3 D.D., with out-lying dirty-grey dots most marked downwards and outwards. There is also a considerable degree of diffuse retinal atrophy. A small retinal haemorrhage is present below the disc at 7 o'clock.

Fig. 27 shows the appearances in the left eye. They are less marked, but the suggestion of retinal atrophy is emphasised by the map-like contours seen in the central region.

Figs. 20–25 illustrate the appearances seen in three elder sisters. The changes seen in one of them (Figs. 24 and 25) bear but little resemblance to those seen in the three other sisters.

FIG. 29.

The patterned exudates characteristic of Doyne's choroiditis are most marked centrally, but also extend peripherally. There is some pigmentation. The patient is aged 31 years.

Fig. 28, illustrating the appearances in an older brother aged 37 years, shows a more advanced stage with the pattern becoming obscured. Ill-defined whitish dots were present in the central areas of the mother, whose visual acuity, in contrast to that of her sons, was unaffected.

Figs. 30 and 31 show somewhat similar appearances seen in a member of another family, two more members of which were affected.

Figs. 32 and 33 show the changes seen in a member of a third family of consanguineous origin.

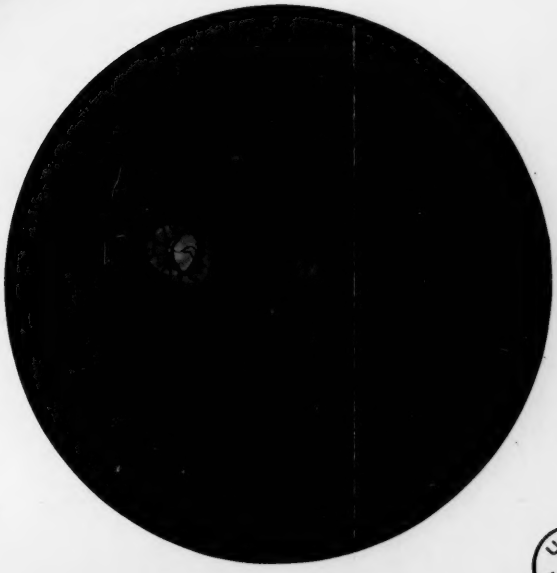

FIG. 35.

Two distinct and typical lesions are present: (1) retinitis pigmentosa in the equatorial region and spreading out peripherally and centrally, and (2) macular dystrophy of the atrophic type with pigment but poorly reminiscent of retinitis pigmentosa.

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The genetic behaviour in the families C., M. and K., tends to indicate an inheritance of the irregular dominant type. The K—r family probably shows regular dominance. In the N. family there was probably recessive inheritance. In the remaining families, the evidence for recessivity is incomplete and the possibility of irregular dominance or dominance with low penetrance cannot be excluded.

As regards the age of onset, the K—r family shows " presenile " incidence (at about the age of 40 years), the K. and B. families illustrate onset in early adult life and both illustrate the fact that a lesion may be present without the patient being aware of it. This is also brought out by the children in the C. family, whilst the M. family appears to show " anticipation " and illustrates the fact that vision need not be severely affected– a finding that also applies to one of the members of the N. family. Judging by the present series of cases the frankly pigmentary type, illustrated by the A. and the K—r families, carries the poorest prognosis as regards central vision. It is clear that it is not justifiable to speak of the macular dystrophies as rapidly and relentlessly progressive, always leading to loss of central vision. Even within the same family the end result is not always the same and the age of onset is not always identical.

As a further illustration of the great range of ophthalmoscopic appearances in the macular dystrophies the following three isolated cases may be briefly described.

Case 1: *Dr. Erich M.*, aged 42 years. Parents first cousins. Patient has a younger brother and sister who are said to be normal. Vision with glasses: R: 6/12, L: < 6/60. The visual trouble dates back to about the age of 20 years, when the left eye began to fail and has progressively got worse. The patient, a man of considerable academic achievement, continues his work quite comfortably with the sight in his right eye. He has been regarded as a case of choroiditis by a number of competent ophthalmologists and has been repeatedly investigated for focal sepsis and syphilis (in England and France) and for tuberculosis (in Germany and Austria). The ophthalmoscopic changes, confined to the macula and the area extending up to the equator, are illustrated in Figs. 32 and 33.

Case 2: *Miss Kathleen T.*, aged 25 years. Parents are first cousins, and have no eye trouble. Family history negative. Patient's only sib, a sister seven years older, is normal.

Personal history.—Sight was noted to be defective at the age of 5 years, and has been worse in dim light all her life. Started school at Birmingham at the age of 6 years, and was referred to a clinic for defective vision. Lived subsequently at Stoke-on-Trent,

saw Mr. P. G. Doyne in 1932, when she was aged 18 years, complaining of night-blindness and defective vision. His findings then were: vision with correction (low myopia) R: 6/24, L: 6/18. The fundi showed diffuse degenerative changes with plaques at both maculae. Peripheral spidery pigment was present. Both fields showed peripheral contraction with large paracentral scotomata tending to merge with the peripheral defect. The Wassermann reaction was negative.

Present condition: Vision with correction 3/36 in each eye. External appearances normal. No nystagmus. Media clear. Vision is too heavily defective to enable the fields to be determined, but they are grossly limited to hand movements. Ophthalmoscopic appearances (Figs. 34 and 35). The discs are slightly pale. The vessels are distinctly narrowed. At the equatorial region there is well established typical retinitis pigmentosa, with pigment changes spreading out both centrally and peripherally. All over the fundus except over a large central area the choroidal pattern stands out. Within the rather darkish and mottled central zone there is a characteristic macular dystrophy of the atrophic type with some pigmentation and whitish dots. The lesions give the impression of slight excavation as if the retinal layer had been removed.

It is clear from the history that these changes were established by the age of 18 years when Mr. Doyne saw her. Unfortunately the earlier records made whilst she was at school could not be traced (Dr. Matthew Burn, Birmingham), so that it is not possible to say that the two lesions co-existed from the beginning.

Case 3: *Mrs. Marion A.*, aged 37 years. Parents are first cousins. The family consists of three surviving daughters of whom the patient is the youngest, and two younger brothers. There were two miscarriages and three children died in infancy. On the history no other member of the family is affected; patient's elder sister was examined and found normal.

Patient first became aware of eye trouble four years ago. Her vision with medium myopic correction was R: 6/12, L: 6/60. It has not deteriorated since. Mr. A. D. Griffith who saw her in 1936 found chorio-retinal atrophy at the right macula with faint mottling extending considerably from the central area to well beyond the nasal margin of the disc. In the left eye there was a deep atrophic patch in the central zone. Now in addition to the macular lesions there is diffuse retinal atrophy over both fundi with considerable unmasking of the choroidal circulation around the discs and diffuse mottling all over the fundi with some grosser pigment changes here and there. In addition the right fundus shows outlying sharply delineated areas of chorio-retinal atrophy

in the upper and outer quadrant (Fig. 36). In the left eye there is considerable vitreous haze. The discs and vessels are normal.

The general appearance suggests a dystrophy rather than in inflammatory lesion. No evidence of infection could be established; the Wassermann reaction is negative. This case may be a further illustration of the diffuse character of macular dystrophy, but it also illustrates the difficulties in the differential diagnosis from inflammatory lesions.

It is of interest to compare the appearances in Cases 2 and 3 with those seen in the A. family which shows in different members the various features seen in these two patients.

(3) The Clinical Features of Macular Dystrophy

(i) *Ophthalmoscopic appearances.*

By definition the macular dystrophies are confined to the macular area, and the view is widely held that the lesion is frequently minimal and generally does not show more than mottling or fine pigmentary disturbances, or at the most an atrophic area. That this is not the case, and that the manifestations are more protean both in appearances and extent is evident from the personally observed cases and from many case reports in the literature in which a considerable range of ophthalmoscopic changes are described within the same family.

(1) *Extent.*—It has already been noted that according to Behr the lesion in macular dystrophies generally covers an area ½-1 D.D., though in one case it extended to 5 D.D. A considerable variation in the size of the central lesion is also shown in the illustration of Alkio's patients.

When a relatively large area is involved, the lesion is generally not sharply defined. There may indeed be a sharply defined

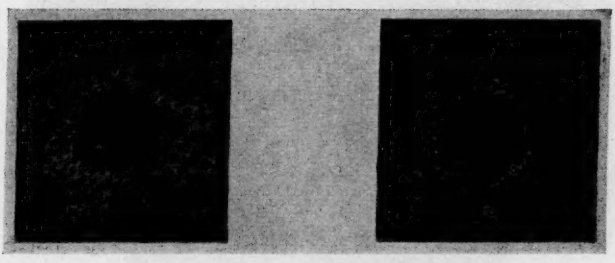

FIG. 37 (WAGNER).

central lesion, but the surrounding degeneration is commonly shown by an ill-defined area carrying white dots. (Jennings, 1909; Stargardt, 1909, 1913, 1917; Feingold, 1916; Caoci, 1935; Grunert, 1903.) The C. family are cases in point, and the illustrations shown by Caoci bring this out clearly. Sometimes the dots are not arranged concentrically around the central lesion but

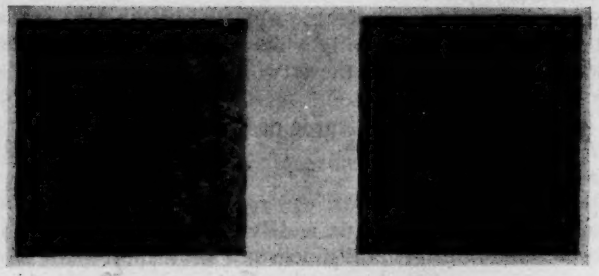

FIG. 37A (WAGNER).

Mottling of maculae in two brothers who also showed lanugo type and distribution of hair.

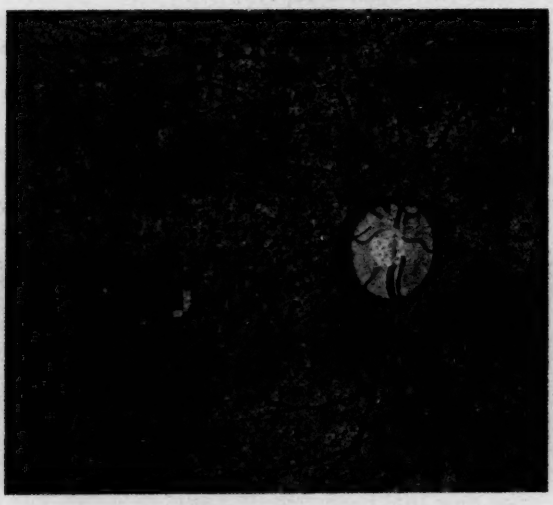

FIG. 38 (GRUNERT).

Mottling of macula. Total colour blindness.

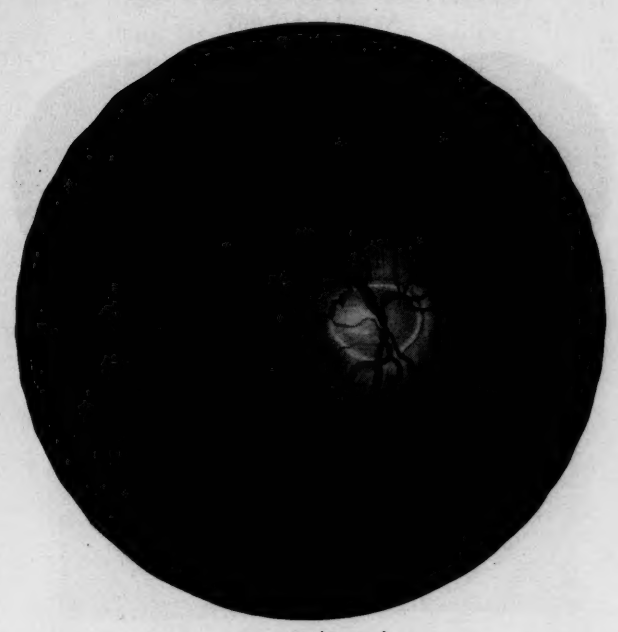

FIG. 39 (PATON).

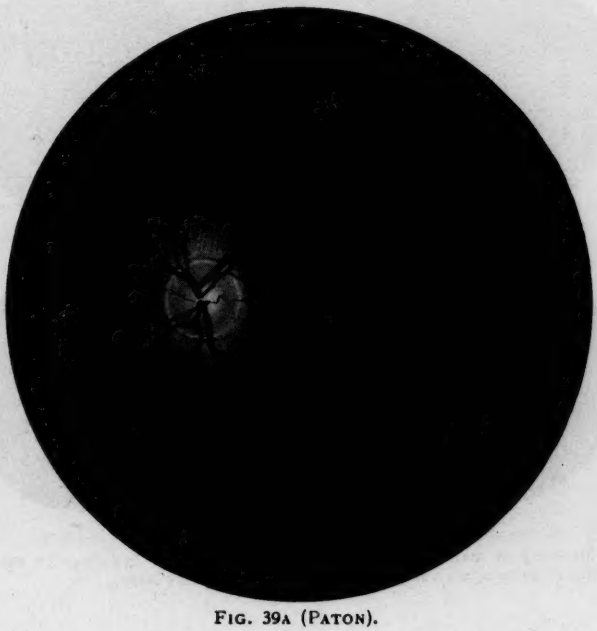

FIG. 39A (PATON).

Mottling of macula (Fig. 39) going on to atrophy (Fig. 39A). Total colour blindness.

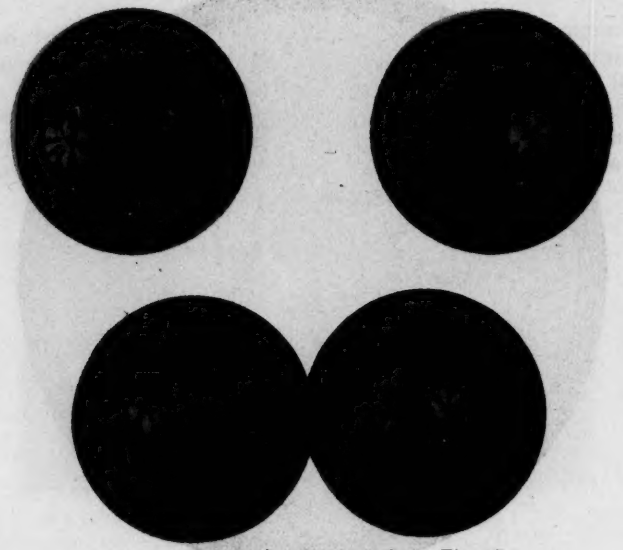

FIG. 40 (DARIER). For legend see Fig. 37.

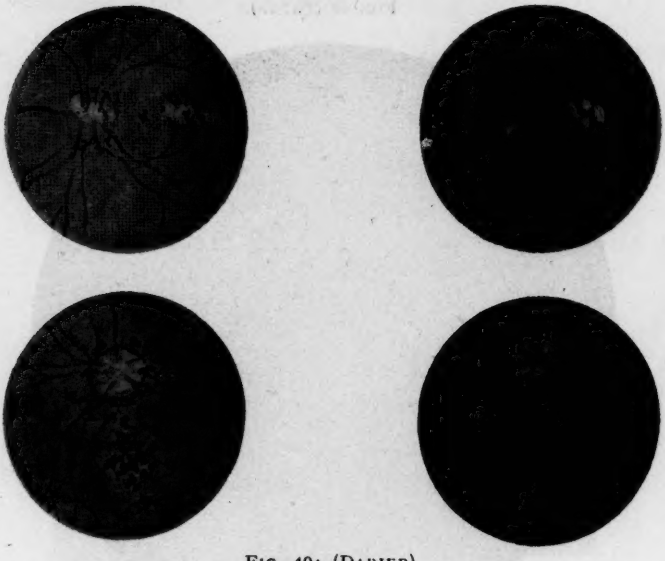

FIG. 40A (DARIER).

Mottling of maculae in two brothers. The lower drawings in each figure show a later stage of development (21 years later).

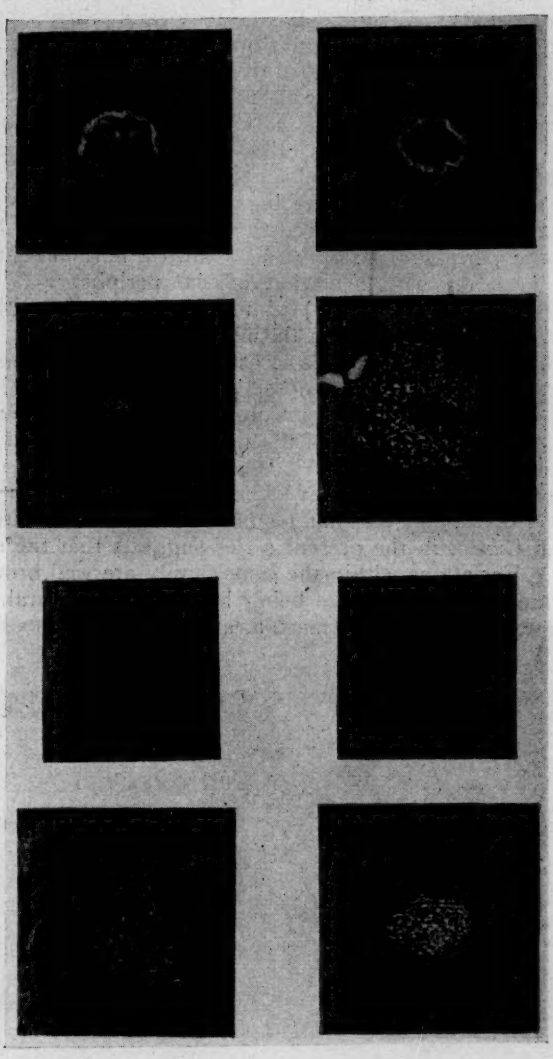

FIG. 41 (BEHR).

Different forms of macular lesions seen in different families.

have an outlying distribution (Stargardt, 1909; Feingold, 1916; Danielson, 1934; Wright, 1935), now and then apparently following a vessel. Of particular interest are those not infrequent cases in which a central lesion is associated with a distinctly peripheral lesion, ranging from peripheral flecks and areas of depigmentation to patches of chorio-retinal atrophy and frank retinitis pigmentosa. (Lang, 1885; Haas, 1897; Klien, 1936; Tillé, 1936; Rieger, 1925; Bollack, 1925; present series, Case 2.) In Tillé's two patients, the peripheral lesion was seen in only one, whilst in Rieger's familial group two members showed both the central and peripheral lesions, and a third a normal central area with patches of depigmentation at the periphery. The cases reported by Liebrecht (1895) of retinitis albescens with heavy central involvement illustrate the least common type of macular dystrophy. One of Liebrecht's cases had been seen 20 years before by Graefe [?Albert] and diagnosed as central chorio-retinitis. The cases of Ibuki and of Danielson probably illustrate the same tendency towards involvement of the whole of the retina. From the illustrations given by Darier it is obvious that when some cases are followed up for a number of years, a lesion that in the first place was essentially macular tends to become more diffuse with time, but Case 2 in the present series suggests that the two may co-exist. Variations within the same family are well brought out by Cavara (1924), the range being between a unilateral macular lesion to extensive bilateral macular and perimacular involvement.

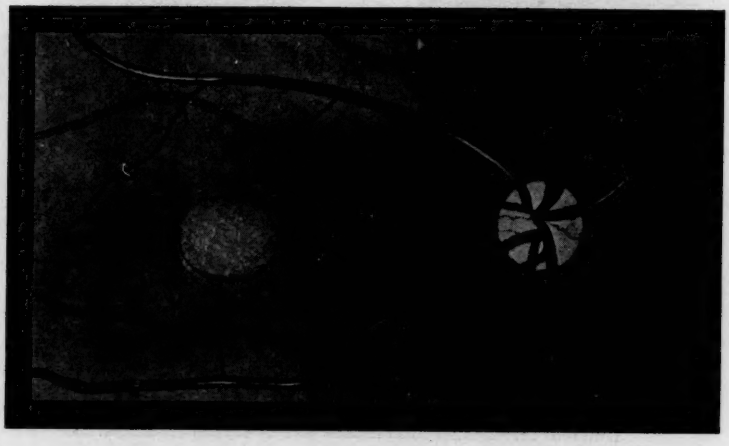

FIG. 42 (BEST).

FIG. 42A (BEST).

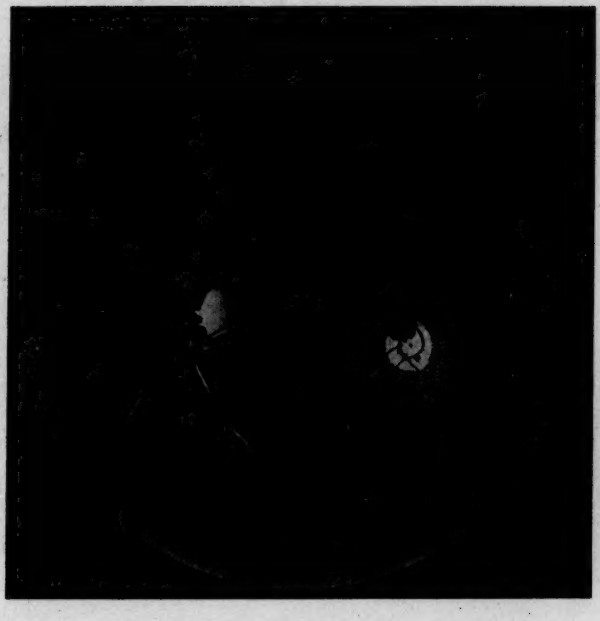

FIG. 42B (BEST).

Appearances seen in the family described by Best (? congenital).

FIG. 43 (STARGARDT, 1909).
Illustrating perimacular involvement.

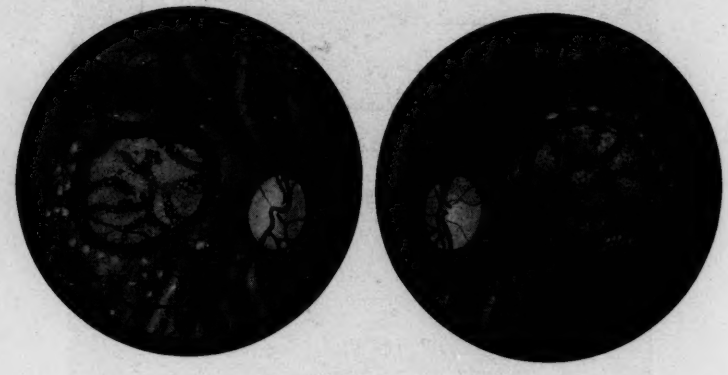

FIG. 44 (STARGARDT, 1917).
Illustrating atrophic reaction with some perimacular involvement.

(2) *Type of reaction.*—No less than the extent does the type of reaction in macular dystrophies depart from the idealised conception. The simplest forms range from loss of macular lustre (Stargardt, 1917; personal observation, C. family) and macular mottling (Wagner, 1935; C. family)—or indeed from no ophthalmoscopic changes at all in early stages, though vision is already affected (Stargardt, 1909; Behr, 1920)—to a well defined area of pigmentary and atrophic reaction surrounded by white dots. (Stargardt, 1909; Behr, 1920; Alkio, 1923) or by a sharply limiting reflex (Danis, 1940). These common forms may show many minor variations: the central lesion may be essentially pigmentary

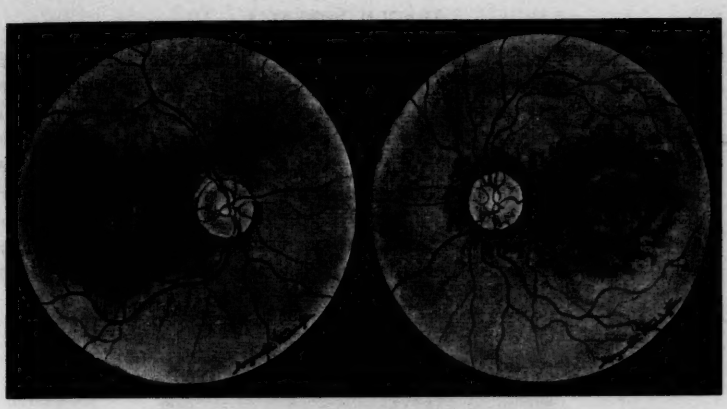

FIG. 45 (CHANCE).
Atrophic reaction. Heavy colour defect.

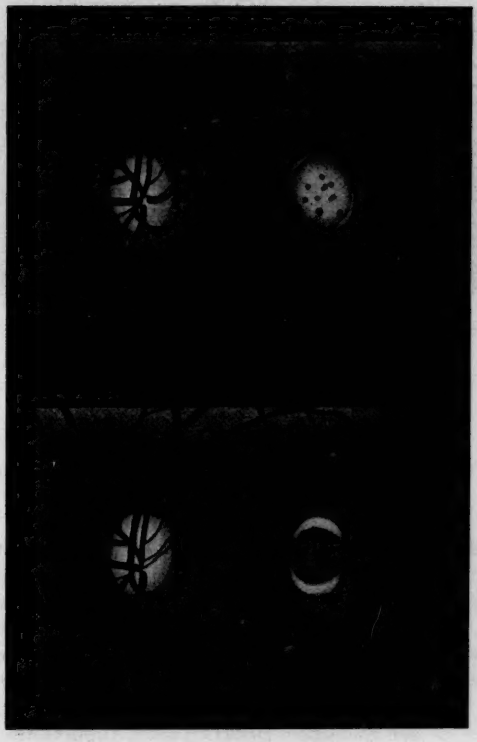

FIG. 46 (MAZZI).
Atrophic reaction in father and son.

in character (Steyn, 1926; Arganaraz and Adrogue, 1928) or essentially atrophic (Chance, 1920; Mazzi, 1934); sometimes there may be a suggestion of hole formation (Stargardt, 1909—personal observation, M. family). Typically such pigment changes as are present do not suggest retinitis pigmentosa, nor do the white dots suggest retinitis punctata albescens.

Less usual forms of reactions are:—

(*a*) Inverse retinitis pigmentosa type: Pigment changes suggestive of inverse (central) retinitis pigmentosa are noted in

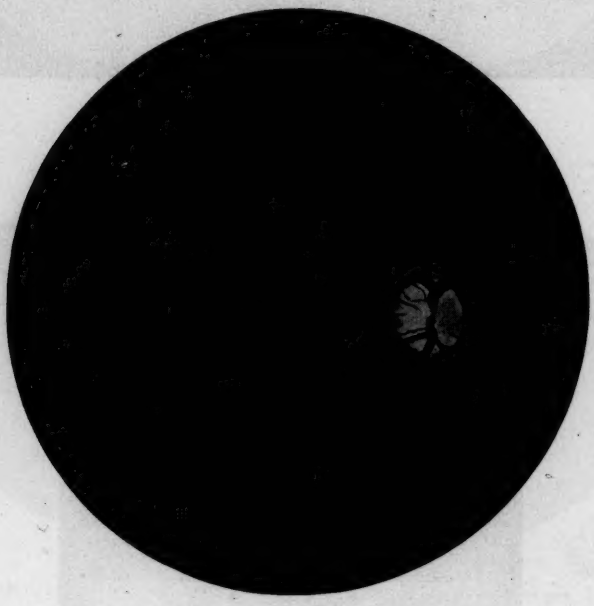

FIG. 47 (v. RÖTTH).

isolated cases by Baumgarten (1907), Davis (1924) and Scheerer (1927). A number of observers have reported familial groups (Stargardt, 1913; Morelli, 1924; Ibuki, 1934; Danielson, 1934; von Rötth, 1930; Waardenburg, 1932). v. Rötth's cases are the most conclusive; a picture strongly reminiscent of central retinitis pigmentosa is shown by a woman aged 28 years, whilst her brother, ten years younger, shows uncharacteristic pigmentary disturbances at the macula. Becker (1921) reports the presence of

bone corpuscle pigment situated peripherally in a 15 years' old boy with macular dystrophy, whilst his sister, three years younger, showed the macular lesion only. A clear approach to the inverse retinitis pigmentosa type is shown by the A. family (Figs. 17-19).

(*b*) Retinitis punctata albescens with heavy central involvement: Retinitis punctata albescens is in itself a none too clear cut entity and this special subvariety is most ill-defined. The familial group reported by Liebrecht in 1895 as cases of retinitis punctata albescens showed a central and paracentral lesion consisting of

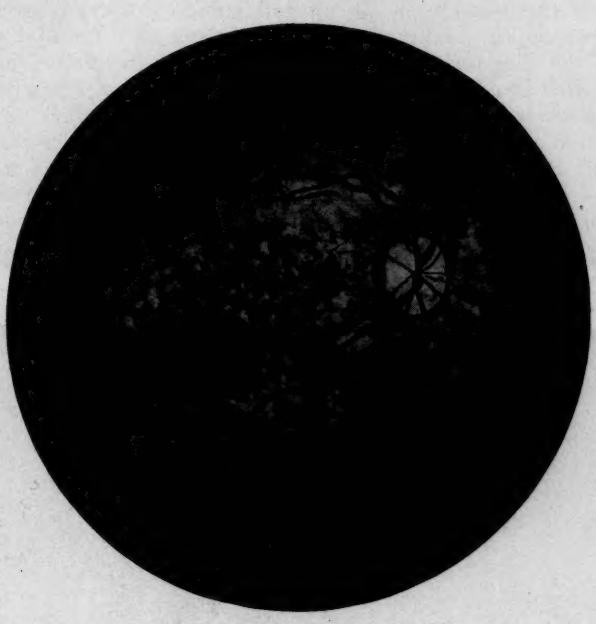

FIG. 47A (V. RÖTTH).

"Inverse retinitis pigmentosa" in a boy aged 18 years, and the more advanced lesion seen in his sister 10 years older.

white dots, and had but little contact with retinitis pigmentosa. Equally inconclusive is the group reported by Morelli (1924). Isolated cases of a rather more convincing character are described by Griffith (1897) and Diehm (1917).

(*c*) Massive central pigmentary reaction: This type illustrated by the K—r family (Figs. 20-27) has little to suggest "inverse retinitis pigmentosa" either on the subjective symptoms or on the ophthalmoscopic appearances, though in the second member

of this family there was some suggestive pigment around the vessels. No similar cases appear to have been reported and this group is of interest as a possible connecting link between the classical type of macular dystrophy on the one hand and the type showing exudative reactions [see (*d*) and (*e*) below] on the other hand.

(*d*) Massive exudative reaction: This is clearly brought out in the M. family and in the N. family previously described. (Figs. 7 to 16.) The massive reaction in these cases conforms more to the conception of an inflammatory focus than to a degeneration or atrophy, and in the absence of a familial distribution the diagnosis of choroiditis would be justifiable in such cases. If it is assumed that the whitish areas of reaction represent decomposition products (?lipoids) of retinal tissue, their ultimate absorption and replacement by atrophic areas is readily explained.

(*e*) "Doyne's choroiditis": This may be regarded as another form of exudative reaction: discrete (and ultimately confluent) type of "exudate." The one histological report available on this condition (Treacher Collins, 1913) does not clarify the issue to any extent.

FIG. 48 (TREE).

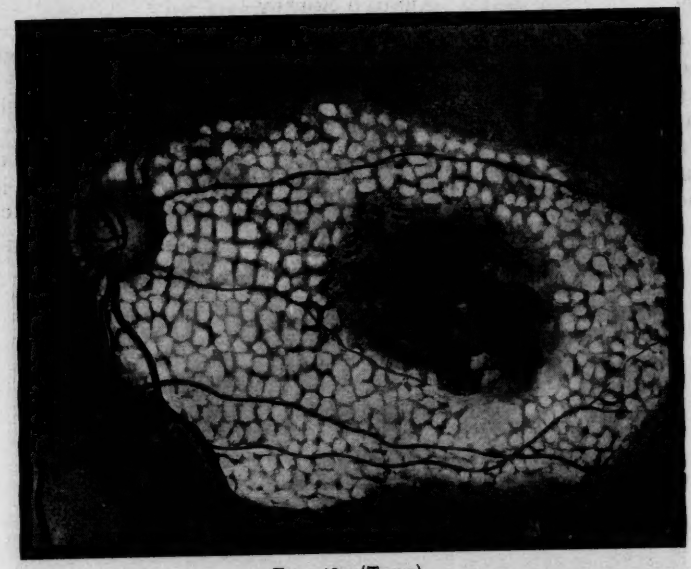

FIG. 48A (TREE).

FIG. 48B (TREE).

(*f*) Rosette figure: This was noted by Brown (1928) in four members of one family.

(*g*) Extensive perimacular involvement: This is seen in various types of reaction, and has no specific significance.

(3) *Symmetry and Familial Stamp.*—Generally it is correct to speak of photographic likeness (Stargardt, 1909) of the lesion in the two eyes. Exceptions do however occur. As already pointed

FIG. 48C (TREE).

out it is doubtful whether the two unilateral cases recorded by Best are admissible. One unilateral case is reported by Cavara, whilst Lewina reports a unilateral lesion in the mother of two boys showing typical macular dystrophy. Some inequality in the development of the lesions in the two eyes is noted by Tiscornia. Within the same family there is generally considerable similarity in the ophthalmoscopic appearances seen in different members. When dissimilar appearances are present (Alkio, Tiscornia, v. Rötth, and the C., M., and A. families) the possibility that different stages are being seen cannot be excluded.

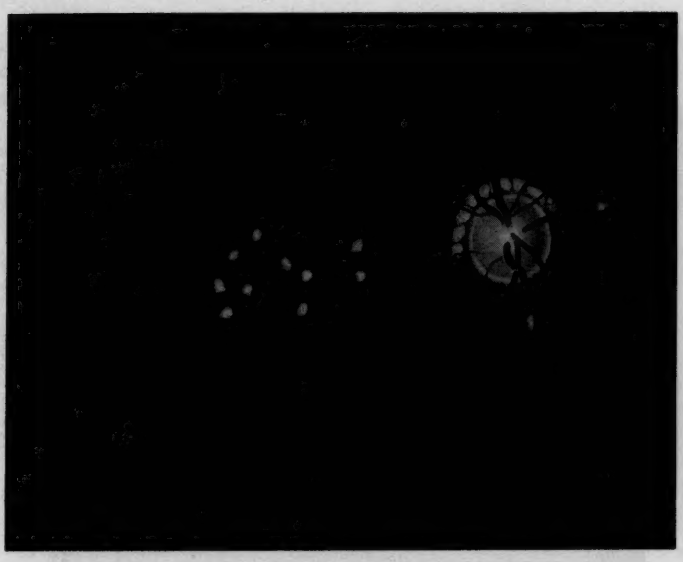

FIG. 48D (TREE).

"Doyne's Choroiditis"—different stages. (Illustrations of Case 4, Case 6, Case 3, Case 7, Case 15. *Brit. Jl. Ophthal.*, Vol. XXI, pp. 74-77, 1937).

FIG. 49 (BROWN).

Rosette figure: "reddish deposits not unlike the colour and setting of the seeds of a red raspberry."

FIG. 50 (JACKSON).

Described in 1903 as familial choroiditis this may possibly be a case of early familial choroidal sclerosis or of extensive perimacular retinal dystrophy.

FIG. 51 (CAOCI).

Extensive perimacular involvement seen in two brothers aged 18 and 15 respectively. These two cases and the family described by Jackson show considerable resemblance to the C family described in this paper.

(4) *Optic Disc.*—Especially in the earlier literature there is much confusion between macular dystrophy and cerebro-macular degeneration. Optic atrophy is frequently reported as an associated lesion of macular dystrophy, but a careful perusal of these cases shows them to be examples of cerebro-macular degeneration. Observations on temporal pallor in genuine cases of macular dystrophy are, however, not uncommon (Stargardt, 1913; Pusey, Blue, Behr, Steyn, Cavara). There is no conclusive

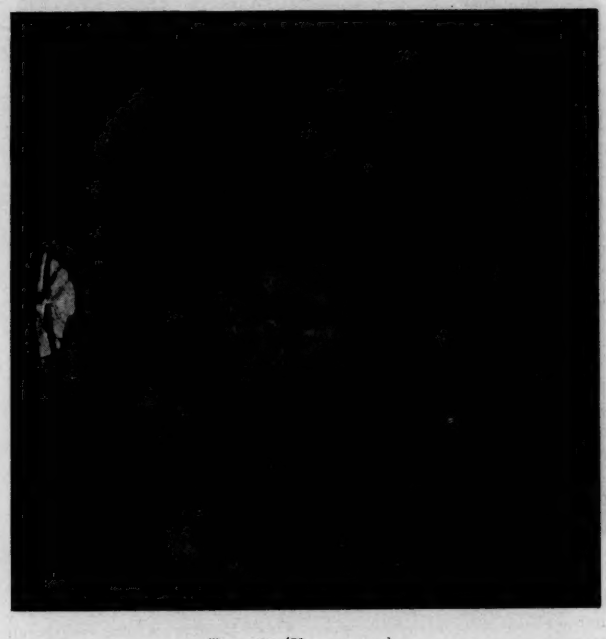

FIG 52 (TISCORNIA).

evidence that this pallor in cases of genuine macular dystrophy extended beyond physiological limits. Pale discs with narrow vessels in a brother and sister aged 4 and 6 years are reported by De Rosa (1925), whose patients had night-blindness, nystagmus and slight microphthalmos. Waxy discs with narrow vessels are reported by Waardenburg (1932) in a familial group (a girl aged 12 years and two boys aged 10 and 3 years respectively) which also showed night-blindness, nystagmus, concentric shrinking of the field and partial colour defect.

Of interest too is the group of a mother and three children (one boy and two girls) reported by R. D. Batten in 1896 as examples of hereditary optic atrophy. The history, the mode of inheritance, and the reference to " fine pigmentation all over the fundus, most marked at macular region " in one child suggest that this group

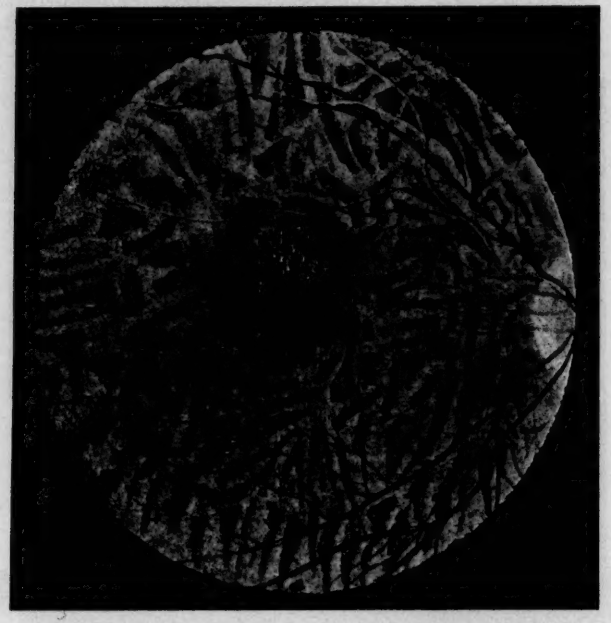

FIG. 52A (TISCORNIA).

Fig. 52 shows the atrophic lesion seen in two brothers and a sister; trouble began in childhood. Fig. 52A shows the appearances (yellowish dots with pigment changes) seen in the mother in whom the eye trouble began at 45 years of age.

may constitute examples of macular dystrophy (then still unrecognised) though such features as slight swelling of the disc and tortuous veins speak against this.

Rather more convincing evidence of optic atrophy in macular dystrophy is supplied by the Jones family studied by the Liverpool School Medical Service (1929, 1933) and by M. D. McQuarrie (1935). Different members of this extensive family have been diagnosed by different ophthalmologists as cases of Leber's disease or of retinitis pigmentosa. The diagnosis of macular

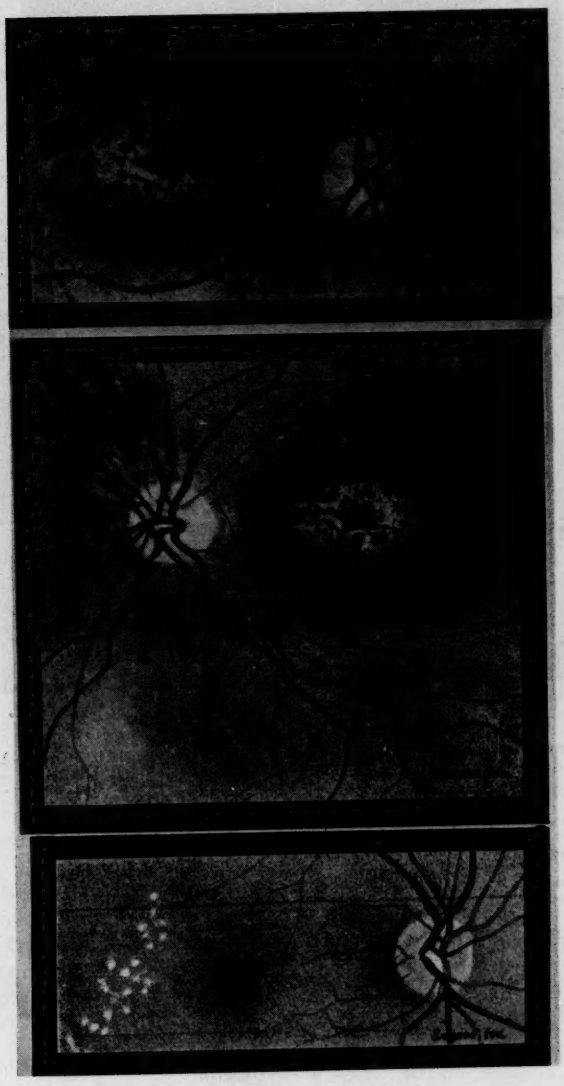

FIG. 53 (FEINGOLD).

FIG. 53A (FEINGOLD).

The range of ophthalmoscopic changes seen in one family. The effect on visual acuity bore no direct relationship to the apparent macular damage.

dystrophy was ultimately suggested. Unfortunately there is no detailed ophthalmoscopic report on this family.

A familial group of optic atrophy setting in early in childhood described by Griscom (1921) is of interest in that some members showed fine granular changes throughout the retina with fine pigment deposits in the macular region. Though regarded by Griscom as examples of Leber's disease, these cases were probably instances of tapeto-retinal degeneration.

(ii) *Age distribution.*

If Best's views are accepted, the extensive family recorded by him and subsequent observers represent a variety of macular dystrophy that is congenital in origin and stationary in character.

In support of the existence of a congenital type, those cases of congenital total colour blindness showing a macular lesion must be mentioned. Cases of the congenital type must, however, be infrequent. Most cases show an onset at about 8-12 years of age; Becker reports one case with onset at 3 years of age; Wagner at 4½ years of age; Urbanek at 5 years of age; Tillé at 6 years of age; in the C. family one child showed macular lesions at 5 years of age; onset at almost any age up to 20 years is not infrequent. (Onset

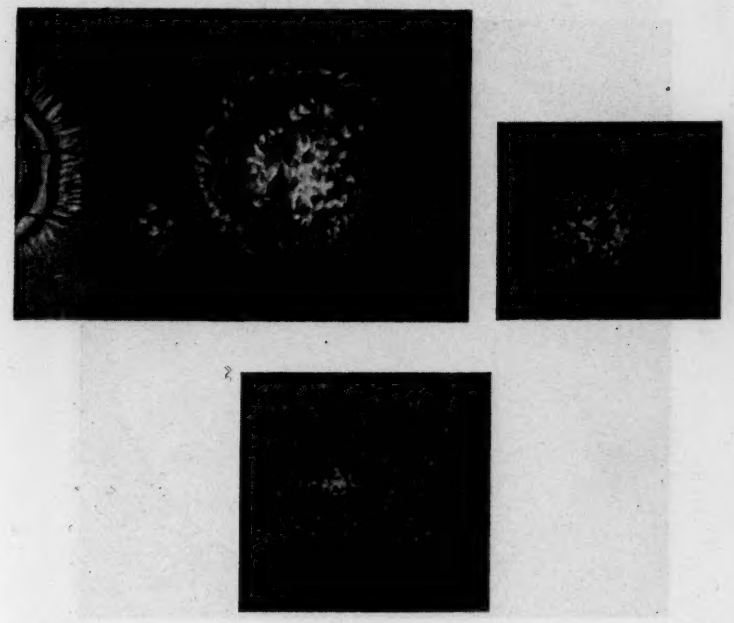

FIG. 54 (ALKIO).

The range of ophthalmoscopic appearance seen in one family.

before the age of 10 years is reported by Dujardin, Darier, Behr, Bollack, Thomson, Wright, Jackson, v. Rötth, Caoci, Danielson, Ibuki; onset between 10 to 20 years of age by Lang, Batten (1897), Blue, Stargardt (1909, 1913, 1916, 1917), Pusey, Clausen, Chance, Becker, Oguchi and Yano, Alkio, Morelli (1924 and 1928), Tiscornia, Lagrange and Peron, Arganaraz and Adrogue, Neame, Burnier, Brown, Klien.)

It does not appear that onset of the dystrophy within a particular family is always at the same age. In fact in most cases there is

some discrepancy as to the age of onset, though the deviation is not extensive. Seven familial groups illustrate the fine line of demarcation between the adolescent and adult type of macular dystrophy. Thus one of the two patients reported by Lang showed an onset at 16 years of age, and his sister (two years older) at 24 years of age. In a group seen by Batten (1926) a woman was affected at the age of 31 years; two younger brothers were affected at 21 and at 12 years respectively. The range was even

FIG. 55 (CAVARA).

wider in the two brothers reported by Klien: the elder brother aged 33 years developed the lesion at 12 years of age, the younger one aged 31 years at 28 years of age. In Clausen's familial group three sibs aged 27 years, 19 years and 15 years showed onset at 23 years, 10 years and 13 years respectively: a feature of special interest in this family was that the lesion was directly inherited, and that the onset in the children showed anticipation for the father was affected at the late age of 41 years. In the family reported by Blue the father was affected at 35 years and his daughter at 12 years of age. Mazzi's record is similar: father

affected at 44 years, son at 22 years of age. The opposite to anticipation is shown in the family reported by Arganaraz and Adrogue: a man aged 34 years had been affected since the age of 30 years; his mother was affected in the left eye since infancy and in the right eye since 30 years of age, and her brother in both eyes since 14 years of age. Apart from these six examples of adult macular dystrophy, cases have been reported by Behr (onset in

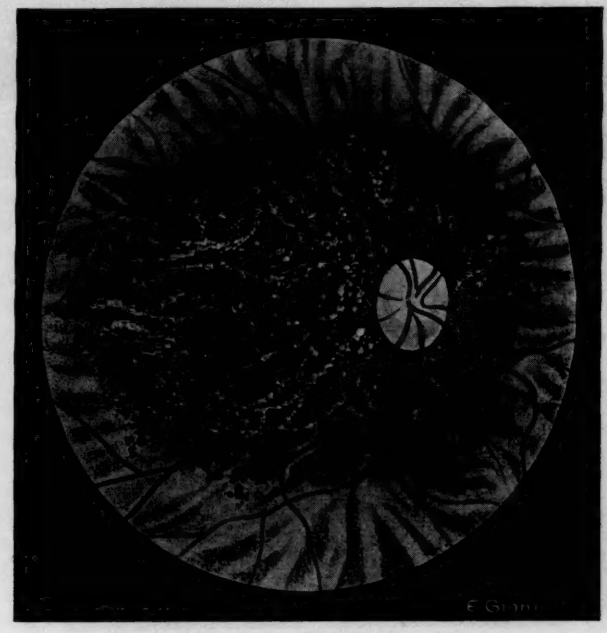

FIG. 55A (CAVARA).

Fig. 55 shows a one sided lesion seen in the youngest member of a family. Fig. 55A illustrates the extensive changes seen in an older brother.

brother and sister at about 25 years of age), Steyn (two brothers at 19 years and 25 years), Feingold (at 22 years in a brother and at 31 years in a sister); the adult type is further illustrated by the K. family.

The literature on the adult type is thus not extensive and it is just as spare on the presenile form and still more so on the senile type. "Presenile" cases are reported by Blue (father and daughter affected at 35 years and 12 years respectively); by Behr (two brothers at 43 years and 53 years; their mother was probably

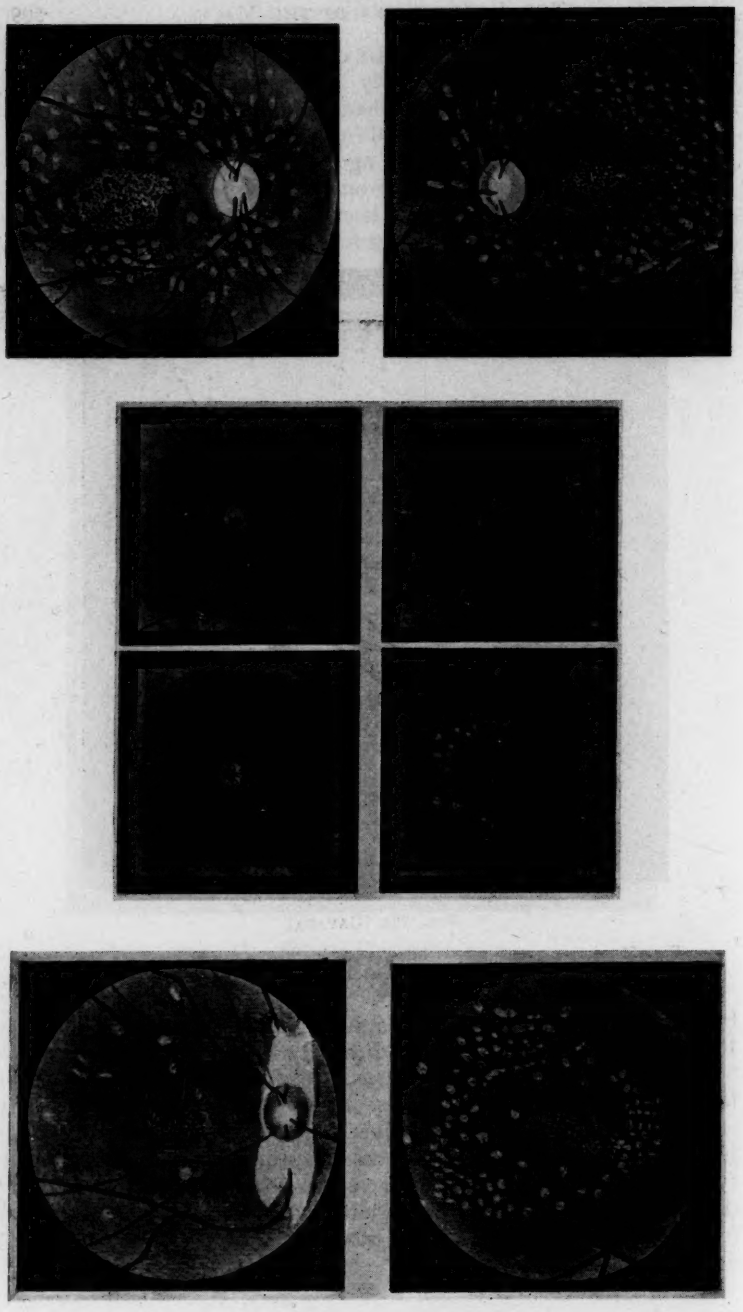

FIG. 56 (MORELLI).

The range of ophthalmoscopic lesions seen in one family.

also affected at the age of 50 years); and by Cavara (at 30 years in two sibs and at 40 years in a third). The " presenile " type was also seen in the K—r family (onset at about 40 years; Figs. 20-27) and in two familial groups already mentioned: the father in Clausen's group was affected at 41 years and in Mazzi's group at 44 years. The evidence for a presenile macular dystrophy, if Behr's and Cavara's cases are excluded, is therefore based on cases of direct inheritance. A brother and two sisters with onset at 50 years in the case of the brother and about 45 years in the sisters, briefly described by Leber, probably belong to this category of cases.

As for senile macular dystrophy, the only records come from Waardenburg. In one familial group three sisters aged 70, 69 and 66 years respectively were affected; the lesion was of the dry atrophic type with white clearly defined dots. In two other familial groups, the history made it likely that other members of the family were affected. A yet further group concerns a man aged 66 years, who showed whitish-yellowish dots at the right macula and his sister, 12 years older, had typical disciform degeneration of the macula of the right eye.

A study of the personally observed cases does not lend much support to any rigid age limit for the appearance of macular dystrophy. The lesion may be present and the patient be unaware of it for many years. Thus in the C. family well marked macular lesions are present in the children whose vision is unaffected to any degree. In the N. family macular lesions have been present in one member for twenty years without giving rise to much trouble. In the K. family visual trouble began in one member at the age of 28 years and in the other at 20 years, whilst the mother is not conscious of any defect, though there are definite, even if mild, fundus lesions. The family described by Feingold illustrates the same features: absence of symptoms even when the macular lesion is fully established.

When speaking of the age of onset of the macular lesions, the age of onset of symptoms rather than of the lesion is being considered. In view of the fact that within the same family the severity of symptoms may vary considerably with different members, and some, though affected, may have no symptoms at all, the conception of photographic likeness as regards onset, appearances and course is rather too schematic.

(iii) *Exciting or aggravating factors.*

Stargardt (1917), notes that in one of his patients vision sensibly deteriorated with each pregnancy. This was also noted in one of the present cases. (Family M.) Mazzi records that in his

group the son—an air force officer—developed macular lesions (haemorrhages during the early stages) and failing vision at 22, after a forced landing.*

(iv) *Symptomatology.*

(1) *Central vision.*—Typically, central vision rapidly declines to about 6/60, and as already noted loss of central vision may indeed occur before the ophthalmoscopic changes are fully developed or at all present. It is this steady deterioration of vision that led Stargardt to name the condition progressive familial macular degeneration, in contrast to Best's cases which were reported as stationary. There is, however, considerable evidence that macular dystrophies do not always show steady deterioration, or indeed heavy loss of central vision—even in cases that began in childhood and had been observed for many years. Thus in one of Behr's familial groups two brothers aged 39 years and 36 years respectively, whose trouble dated back to the age of 8 years, had vision of 6/18 and 6/12 respectively. Thomson's group in adult life showed vision of about 6/24 though the condition was of many years' standing. Sometimes the patient is unaware of any serious visual disturbances though the macular lesion may be fully developed; thus the three patients reported by Feingold, two sisters aged 38 years and 36 years respectively and their brother aged 26 years, had vision ranging from 5/10 to 5/6. Similarly Morelli noted macular lesions with unaffected vision in the two daughters (aged 15 years and 14 years) of an affected father. One of Rieger's patients, a man aged 38 years had 6/9 and 5/6 vision though a younger brother, aged 25 years, had only C.F. at 2½-3 m. and showed ophthalmoscopically the more marked lesion. In the N. family, the brother had practically full vision in spite of well marked lesions observed for 20 years.

As with the ophthalmoscopic appearances, the two eyes are not always equally affected visually. One of Steyn's patients had vision of 4/60 in one eye and 6/12 in the other. The group reported by Tiscornia, similarly showed considerable difference of visual acuity in the two eyes.

Rieger's cases, already mentioned, illustrate the fact, also brought out by the G. family reported by Morelli, by Brown's patients, and by the N. family in the present series, that within the same family not all members are equally severely affected, though generally this is the case.

* In a new familial group seen after this paper was completed, a girl aged 17 years showed the classical type of macular dystrophy, which had developed at the age of 14 years. Her twin brother has recently developed an identical unilateral lesion after receiving a blow on the eye with a tennis ball.

The familial group reported by Clausen suggests that not only is there " anticipation " in cases of direct dominant inheritance, but that the children are more severely affected. Thus the father's vision at 53 years was C.F. at 1 m. in the right eye and 5/15 in the left. The children on the whole showed heavier defects. On the other hand the father in Blue's group, at 43 years had 6/36 and 6/60 and the daughter at 18 years vision of the same order (6/60); seeing that in the case of the father the onset dated from the age of 35 years and in the daughter at 12 years, it is possible that ultimately the daughter may prove to be the more heavily affected. In Mazzi's group the father's vision at 51 years (onset at 44 years) was 4/10 and 3/10, whilst the son at 25 years (onset at 22 years) had 5/10 and 10/10.

A considerable proportion of the cases with relatively good vision appear to belong to the group of patients who were affected in adult life (Clausen, Rieger, Feingold), but that the adult type can run a rapid course is shown by Behr's group. At the age of 25 years vision was 5/6; within 6½ years it had declined to 6/36. Similarly Steyn's patient aged 28 years (onset at 25 years) had 3/24 and 3/12. A fairly rapid course in the presenile type is illustrated by the K—r family.

(2) *Field defect.*—(*a*) Peripheral contraction: This has been noted only exceptionally and only in those cases in which the ophthalmoscope shows peripheral involvement in addition to the central lesion. Lutz records some peripheral contraction in cases with macular lesions only, but as central vision was poor, an error of observation is not unlikely.

(*b*) *Central Scotoma*: Positive scotomata do not appear to have been reported. The absence of negative scotoma is occasionally noted. (Stargardt, 1909; Morelli, 1928; Jung. Personal observation).

At different stages, scotomata of different types are recorded. A relative central scotoma in one eye and an absolute scotoma in the other is noted in one patient by Lagrange and Peron. Absolute scotoma for colours, generally red and green, and a relative scotoma for white is a frequent observation (Stargardt, 1909, and Becker), as is absolute scotoma for colours and white (Bollack, Tillé).

(3) *Colour Vision.*—The development of central scotomata for colours seems occasionally to extend to the complete loss of colour vision, as reported by Clausen, whose patients had good colour vision before the onset of the macular dystrophy. On the other hand Behr reports colour defect ranging from red-green blindness to total colour blindness as a linked congenital anomaly, not the result of the macular dystrophy. In one of his families some

affected members had partial colour blindness, whilst others had normal colour vision. This was also seen in the A. family of the present series. Colour anomaly is certainly not a constant feature in macular dystrophy, and in the family reported by Feingold there were colour anomalous persons with normal fundi. But the frequency with which partial colour anomalies (Best, Behr, Rieger, Halbertsma, personal observations, etc.) have been reported cannot be fortuitous. Jung indeed holds that in the family with Best's disease congenital colour anomaly is no more frequent than in the general population, but nevertheless it is difficult to believe that the not uncommon association of two such rare lesions as total colour blindness and a macular dystrophy can be altogether fortuitous.

The literature contains a considerable number of isolated cases of total colour blindness with macular lesions. (Nagel, 1902; Uhthoff, 1902; Grunert, 1903; May, 1908; Gertz, 1912; Velter, 1923). Familial groups have been reported by Nettleship, 1880, Hessberg, 1909, Behr, 1920, Chance, 1920, Alkio, 1923, and Sorsby, 1934. The macular lesions in these cases of colour blindness have ranged from doubtful haze or congestion of the yellow spot (Nettleship) to slight pathological changes (Uhthoff, Hessberg, Sorsby) to fully established atrophic lesions (most of the other observers).

There are also suggestive familial groups from Hess, 1902, Grunert, 1903, Bjerrum, 1904, and Bunge, 1936. The brother and sister reported by Hess showed macular lesions exceptionally marked in the right eye, and but feebly developed in the left. In Grunert's group the sister showed definite macular lesions, but the brother's fundi were normal apart from a yellowish spot of doubtful significance above the left macula. Bunge's cases referred to two sisters and have the special interest in that the elder sister showed the macular lesion only and had keratoconus as an associated lesion, whereas the younger sister had a normal macula but the rest of the fundus was of the pepper and salt type.

(4). *Light sense.*—Day-blindness: Records of tests for light sense are not frequent in the literature, nor always easy to follow owing to the multiplicity of instruments used. Lutz reports a doubtful increase in light minimum. No increase in dark adaptation is recorded by Stargardt (1917). There is certainly no obvious night-blindness in the recorded cases in the literature, and in many cases the presence of a central scotoma leads to better vision at dusk (Lutz, Oguchi and Yano). Frank day-blindness is of course recorded in some of the cases of total colour blindness (Alkio, Sorsby, 1934). One of Chance's patients had day-blindness, but his sister who had severe colour blindness, was free from this.

Night-blindness in an unaffected member of the family is noted by Behr. Von Rötth's patients—clearly presenting " inverse retinitis pigmentosa "—showed diminished dark adaptation and saw worse at night. There was no night-blindness in the A. family reported here.

(v) *Associated Defects.*

Surprisingly little in the way of associated anomalies is reported in the literature and there were none in the cases observed personally. Mental defect is reported by Morelli (1924 and 1928), Wright and Ibuki, but many observers stress the normal intelligence of their patients. Familial deafness of nerve type is reported by Morelli (1928), whilst Alkio noted cochlear deafness in an otherwise normal child of one of his patients. Deaf-mutism in two of four paternal cousins is noted by Urbanek. Post-capsular lens opacities are noted by Danielson in one of his patients (aged 38 years). Blue-dot opacities were noted in an unaffected mother and in her affected daughter by Morelli (1928) and in four cases by Ibuki, who also found unilateral vitreous opacities in two patients. Neuro-retinitis and retinal detachment in one eye in one of his patients was noted by Thomson, and nystagmus in a familial group by Waardenburg (1932). Lanugo type and distribution of hair was reported by Wagner, and some vague cardiovascular anomalies by Pusey, who held the macular lesion to be vascular in origin. Dolichocephaly was present in Wright's cases. Keratoconus was present in one of Bunge's patients and in one of the cases observed personally (family F.); microphthalmos and macular lesions were noted by De Rosa in 1925.

In groups doubtfully belonging to the macular dystrophies Borsellino (1935) reports macular lesions in a familial group showing microphthalmos and optic atrophy; one member also showed keratoconus. Extensive associations are also reported by Rossi (1931), who found not only macular changes, but peripheral lesions, hypogenitalism and calcification of the meninges and pituitary.

Much the most significant associated lesions are some degree of optic atrophy and colour anomalies, and as already noted they are not frequent, and certainly not constant. In the totally colour blind nystagmus is frequent.

(vi) *Genetic Aspects.*

The occurrence of a macular lesion over several generations in the widespread family studied by Best and subsequent observers establishes the dominant mode of inheritance in at least this form

of macular affection. This also applies to the familial groups of Doyne (Tree). For the macular dystrophy of the more classical type, many instances of dominant transmission have been recorded since Blue reported the affection in a father and daughter (Table IV).

Recessive inheritance is, however, not uncommon. This is apparent from the " familial " character of the affection and the high incidence of consanguinity in the parents. (Table I.) Where inheritance is dominant it is not always in a direct line. A healthy daughter of an affected family having an affected son is noted by Morelli (1924). An affected son and daughter of an unaffected mother, whose two sisters and a brother were affected, is shown by the C. family. Indirect inheritance is further illustrated by the M. family. Any attempt at classifying the macular dystrophies into genetic types with a clear-cut corresponding ophthalmoscopic type, breaks down.

In a series of sixteen Japanese pedigrees collected by Komai consanguinity was present in almost all. Komai holds that the condition though a simple Mendelian recessive, may show itself in the heterozygous state in exceptional cases.

TABLE I

Consanguineous Sibships

AUTHOR	Degree of consanguinity in parents	Sibship			Number affected			Remarks
		M.	F.	P.	M.	F.	P.	
Behr	Uncle and niece	1	2	–	1	1	–	
Caoci	First cousins	1	3	4	1x	1x	–	x Sole survivors; all but one died under 15
Dujardin	First cousins	3	2	–	2x	–	–	x ? 3
Feingold	First cousins	6	4	–	1	2	–	
Haas	" Remote "	–	–	13	2	–	–	
Hessberg	Unstated	2	1	1	2	1	–	Mother had three normal children by a 2nd marriage
Jackson	Third cousins	(2)	6	–	–	2	–	
Neame	First cousins	–	3	–	–	2	–	
Oguchi and Yano	Unstated	–	–	–	2	–	–	
Wagner	Second cousins	3	2	(1)	2	–	–	
Present series N. family	First cousins	–	–	–	1	1	–	

( ) = Still birth, died at birth or died young.

TABLE II

Non-consanguineous sibships with affection not known in ascendants

AUTHOR	Sibship			Number affected			Remarks
	M.	F.	P.	M.	F.	P.	
Behr	7x	4	–	2	1	–	x Male, with normal fundi has night-blindness
,,	3	3	–	2x	0	–	x Male, died at 8 affected
				2*	–	–	* Mother apparently affected at 50
Chance	5	2	–	1	1	–	
Kleefeld	3	5	–	3	2	–	
Liebrecht	2	3	–	2	2	–	
Lutz	3	6	–	0	4	–	
Rieger	3	1	–	2	(?1)	–	
Stargardt (1909)	1	4	–	1	4	–	
,, and Behr (1920)	4+(1)	0	–	3	–	–	
Stargardt (1913)	2	1	–	2	1	–	
v. Rötth	1	3	–	1	1	–	
Waardenburg (1932)	–	–	12x	2	1	–	x 5 died in infancy
Wright	3	3	–	3	–	–	
Present Series							
A. family	2	2	–	1	2	–	
B. ,,	6	3	–	1	2	–	
F ,,	–	–	18	–	2	–	

( ) = Still birth, died at birth or died young.

TABLE III

Sibships with no information given on consanguinity.
Affection not known in ascendants

AUTHOR	Sibship			Number affected			Remarks
	M.	F.	P.	M.	F.	P.	
Alkio	–	–	–	3	1	–	A normal sister has daughter aged 5 with mental defect and atypical retinitis pigmentosa. An affected male has a deaf child (cochlear)
Batten (1897)	2	1	(3)	2	–	–	

TABLE III—*continued*

AUTHOR	Sibship			Number effected			Remarks
	M.	F.	P.	M.	F.	P.	
Batten (1926) - -	5	1	–	2x	1	–	x ? 3
Becker - - -	–	–	5	2	1	–	
,, - - -	–	–	–	1	1	–	
,, - - -	–	–	–	2	2	–	
Behr - - - -	–	–	5	1	1	–	
Bollack - - -	3+(1)	3	–	1	2	–	
Brown - - -	3	2x	–	3	1	–	x One under 6
Burnier - - -	–	–	11	2	2	–	
Cavara - - -	–	–	7	2	1	–	
Danielson - - -	4	2	–	1	1	–	
Danis - - -	–	–	–	1	1	1	
Darier - - -	0	4	1	0	2	–	
,, - - -	6	1	–	3	0	–	
De Rosa - - -	–	–	5	1	1	–	
Fesus - - -	–	–	–	–	2	–	
Hess - - - -	–	–	–	1	1	–	
Ibuki - - - -	–	–	6	–	–	5	
Jennings - - -	–	–	–	1	2	–	
Klien - - -	–	–	–	2	–	–	
Lagrange and Peron -	3	(1)	–	2	–	–	
Lang - - - -	1	2	–	1	1	–	
Leber - - -	1	3	–	–	2	–	
Letchworth - -	–	–	–	1	1	–	
Neame - - -	2 (1)	1	–	1	1	–	
Nectoux - - -	–	–	–	1	1	–	
Nettleship - -	6x	5	–	2	4	–	x Two died young
Paton - - -	–	–	–	1	1	–	
Pusey - - -	3	5	–	1	4	–	
Stargardt (1916 and 1917)	3x	2x	–	1	1	–	x One female died at 7; One male died at 10
Steyn - - -	3	1	–	2x	–	–	x ? 3
Thomson - - -	4	2	(2)	4	0	–	
Tillé - - - -	5	3	–	0	2	–	Two out of four paternal cousins (females) are deaf mutes ' Une collaterale est atteinte ''
Urbanek - - -	1	1	–	1	1	–	
Waardenburg (1936) -	–	3	–	–	3	–	
,, (1938) -	–	–	–	1	1	–	

( ) = Still birth, died at birth or died young.

TABLE IV

Sibships with macular dystrophy in ascendants

AUTHOR	Sibship			Number affected			Remarks
	M.	F.	P.	M.	F.	P.	
Arganaraz and Adrogue	-	-	-	1	1	-	
				1	-	-	
Behr	3	3	-	2x	-	-	A female cousin is affected. x A daughter of one of these affected males shows macular dystrophy. Anamnestic history of many more members in collateral branches affected
Blue	4	2	-	1		-	
	0	2	-	-	1	-	
*Best-Vossius-Weisel-Jung	-	-	-	-	-	-	
Clausen	-		-	1	-	-	
			6	1	2	-	
*Gasteiger	4	6	-	1	2	-	Subsequent generations direct and indirect inheritance
*Halbertsma	-	-				-	Extensive family with colour blindness. Some have macular defect as well. Males only affected
Lewina	-	-		2	-	-	The mother has a somewhat similar lesion confined to one eye only
Mazzi	-			1	-	-	
				1		-	
*McQuarrie	Dominant inheritance over 4 generations			19	17	-	
Morelli (1924)	-	-	8x	4	1		x A healthy daughter has an affected son
				-	2xx		xx Daughters of one of the affected sons
Morelli (1928)	-	-	6	2	1	-	
				1	2	-	
				1x	-	-	x Son of one of the affected sisters
Ogata	-	-	-	1y	-	-	Father (y) affected.
				1x	-	-	x Parents second cousins.
Tiscornia	-	-	-	-	1	-	
	-	-	11x	2	1	-	x Three died early
*Tree	-	-	-	-	-	-	" Doyne's choroiditis "
Present series							
C. family	2	3	-	1	2	-	Father probably affected. An unaffected daughter has an affected boy and girl
K. ,,	5	2	-	2	-	-	Mother mildly affected
*M. ,,	-	-	-	-	-	-	
K-r. ,,	5	5	-	1	4	-	Father probably affected

* See originals for extensive trees. – ↓ Indicates parental relationship.

As already noted anticipation has been recorded by Blue, Clausen, Mazzi and in the personal observations. There was no obvious anticipation in Behr's cases and in those of Arganaraz and Adrogue.

(4) Discussion

(i) *The ophthalmoscopic lesion.*

From the analysis of the literature and the personal cases reported it is clear that the designation of macular dystrophy is too narrow. The loss of central vision present in most cases emphasizes the central site of the affection, but in many cases (such as in those of Best) the lesion is extramacular leaving good vision, and in not a few the macula is spared even when the central area seems heavily involved. Even more significant is the considerable extension beyond the central area seen in many instances. To speak of macular dystrophy in such cases is almost like designating retinitis pigmentosa " equatorial degeneration of the retina " : an early and striking change rather than the whole picture would be stressed. It is worth recalling that some cases of retinitis pigmentosa in their late stages show considerable central involvement, others show such involvement earlier on (Carruthers, 1915; Spare, 1928; Pavia and Dusseldorp, 1934); in some, hole formation at the macula is seen (Perera, 1938) and that cases of retinitis pigmentosa have been described in which the lesion consisted of a girdle of pigment enclosing the disc-macular zone (Wittmer, 1908; Lafon, 1913). These observations together with those on the inverse retinitis pigmentosa type of macular dystrophy constitute intermediate cases towards Case II in the present series showing clearly the association of typical retinitis pigmentosa with macular dystrophy.

The conception of an atrophic lesion with scattering of pigment is also too narrow. It is obvious that an " inverse retinitis pigmentosa " exists, and that furthermore an " exudative type " and a type with heavy central pigmentary changes—as shown in this paper—have to be considered. From the exudative type to the exudates of Doyne's choroiditis is no far cry. The evidence of a haemorrhagic type (Mazzi, Waardenburg) is not as convincing. Evidence of involvement of the optic nerve in cases of macular dystrophy is also unconvincing.

(ii) *Disturbances of function.*

Central vision.—It is important to recognise that the affection is not always relentlessly progressive till central vision is lost, and that even within the same family the prognosis varies considerably. A well developed ophthalmoscopic lesion is compatible with retained central vision.

Central and paracentral scotomata and light sense.—The retina in the central area may remain remarkably sensitive to light perception and to the recognition of colours. In some cases day blindness arises from the central scotoma; in others it appears as a congenital lesion.

Colour vision.—A frequent association of macular dystrophy with colour anomalies is undoubted. The congenital cases of total colour blindness with macular lesions and the presence of colour anomalies in the unaffected sibs of patients with macular dystrophy raises the possibility of linkage of the two disturbances, but the more likely explanation is that the colour anomaly is the direct consequence of the retinal lesion. A feature of considerable theoretical interest is the occasional association of day-blindness and total colour blindness with typical retinitis pigmentosa. (Nettleship, 1880; Klainguti, 1923).

(iii) *The conception of macular dystrophy.*

The conception of macular dystrophy has, therefore, to include a wide range of anatomical and functional disturbances. At the one extreme are the congenital cases with such gross functional anomalies as day-blindness and total colour blindness, at the other mild central lesions observable ophthalmoscopically but functionally silent. In between these there is a wide range of lesions with an onset at ages ranging from infancy to senility, with varying severity of functional disturbances, and an extensive variety of ophthalmoscopic appearances extending from macular mottling to widespread involvement of the fundus and showing reactions of an atrophic, exudative, pigmentary or haemorrhagic type.

The grouping together of frankly congenital affections such as the macular lesions seen in congenital total colour blindness and possibly in Best's familial group on the one hand, with abiotrophic affections making their appearance at almost any period of life on the other hand, finds its justification in the undoubted occurrence of anticipation in some cases of dominant inheritance. Granted this, there is no logical barrier against regarding ante-natal lesions as part of the continuous chain of post-natal affections. Indeed, to the embryologist, birth is but a dramatic phase in development.

(iv) *Differential diagnosis.*

If the cases described by Best and those by Doyne are regarded as constituting clinical variants of macular dystrophy and the conception of macular dystrophy is extended to cover paracentral lesions and reactions of the retinitis pigmentosa type and the

exudative type as well as the atrophic type, the multiplicity of independent central familial retinal affections becomes reduced considerably. The diagnosis has still to be made from congenital macular coloboma, angeoid streaks and familial central choroidal sclerosis. As for macular coloboma no difficulty in diagnosis is likely to arise, for the extensive destruction of the choroid and the excavation which are characteristic of the colobomatous lesion are absent in macular dystrophies. As for angeoid streaks, the picture is so characteristic in the uncomplicated cases and the complications of haemorrhages and exudates are so different from the appearances seen in macular dystrophy, that difficulties in diagnosis are again hardly likely to arise. The possible associated lesions of skeletal anomalies in macular coloboma and pseudoxanthoma elasticum in angeoid streaks are also factors to be considered. A distinctly more difficult problem is presented by central choroidal sclerosis. In fact several cases reported as macular dystrophy may quite likely have been cases of choroidal sclerosis. Hutchinson's group in 1875, Mager's in 1898 (read in abstract) and possibly also Jackson's group (1903), probably fall into that category, as Haas's group in 1931 definitely does belong here. One of Waardenburg's senile familial groups was probably also a case of choroidal sclerosis. In the fully established lesion a difficulty in diagnosis could hardly arise, for the conversion of the exposed choroidal vessels into white streaks is characteristic and unmistakable. Early stages of choroidal sclerosis are, however, not well recognised and it has been shown elsewhere (Sorsby, 1939) that they may take the form of mild changes in the central area simulating central choroiditis. It is at this stage that the differential diagnosis is difficult, if there is no help from the appearances seen in other members of the family.

Several central lesions of a non-familial character require differentiation from macular dystrophies.

(*a*) *Retinitis Centralis Serosa.*—Ophthalmoscopic appearances that go under the names of pre-retinal oedema, retinitis centralis serosa, retinitis serosa disciformis, central angiospastic retinitis and other designations simulate an early stage of macular dystrophy. The unilateral character of this lesion, its onset in adult life, the absence of a familial history, the frequent presence of a positive scotoma and the abruptness of onset, all establish a picture which generally should be sufficient to distinguish it from the macular dystrophies. (Gifford and Marquardt, 1939.)

(*b*) *Traumatic Macular Lesions.*—Ophthalmoscopically the appearances frequently simulate macular dystrophies. The history and the unilateral character of the lesion will in most cases establish the diagnosis.

(*c*) *Central Chorio-retinitis.*—When bilateral, a conclusive differential diagnosis is sometimes impossible and case reports in the literature emphasize this difficulty (Hughes, 1931; MacRae, 1934). In a case reported by Russ Wood and Anderson (1922) a dystrophy was excluded because of a response to antisyphilitic treatment. Even in familial cases an inflammatory origin (syphilitic) has been assumed by French observers. (Morax, 1925.)

In most cases an inflammatory central lesion will present a rather less regular ophthalmoscopic picture for each eye separately, and a tendency to dissimilarity as between the two eyes. Pigment changes are also likely to be more extensive, though the K—r family illustrates how these criteria can all be fallacious. Case 3 in the present series is a further illustration of the difficulties in differential diagnosis.

(*d*) *Relationship to Cerebro-macular Degeneration.*—The macular lesion in some cases of macular dystrophy is so similar to the changes seen in cerebro-macular disease, that some confusion arose in the earlier literature on the subject, Oatman, Stargardt and others speaking of two types: macular lesions with psychic disturbances and those without. This confusion was facilitated by the eponymal background of the description of these affections, R. D. Batten having described the macular dystrophy in 1897 and F. E. Batten cerebro-macular degeneration in 1903. There is, however, no reason to assume any association (Sorsby, 1937) and the evidence advanced by Togano (1930) that there are intermediate forms is inconclusive. The progressive nervous lesions that are seen in cerebro-macular degeneration do not occur in the families with macular dystrophies, fortuitously associated mental defect being the most that has been observed in macular dystrophies. Moreover there is no evidence that in families with cerebro-macular disease one member will escape with the macular lesion only. That there is no genotypical unity between these two affections is further brought out by the genetic behaviour of the two diseases. Sjögren has shown that cerebro-macular degeneration is transmitted as a simple Mendelian recessive. Macular dystrophy has a distinctly more complicated and more varied behaviour.

The familial group reported by Bonnet and Colrat is of some interest in this connection. A woman aged 23 years showed macular lesions of the dystrophy type, and also neurological signs suggestive of disseminated sclerosis. Her mother, 20 years older, had failing vision for five or six years, retinitis pigmentosa without night blindness but with macular lesions; she could not walk, was mentally alert, and one of her sisters had died at 28 years blind and paralysed. This unconvincing example of macular

lesions with neurological signs but no psychic disturbances emphasizes the lack of unity between cerebro-macular degeneration and macular dystrophy.

(v) *The nature of macular dystrophies.*

No histological studies of macular dystrophies are available, if Treacher Collin's report on a case of Doyne's choroiditis and an incompletely reported study by Larsen of the macula in total colour blindness are excepted. These histological studies do not take the matter very far, so that there is no solid basis for the understanding of the pathology of macular dystrophy. At this stage only conjectures can be put forward. The available clinical evidence seems to point to the macular dystrophies being essentially a degeneration of the cones and that the process is not confined to the macula though for anatomical reasons it is most marked there. Such a reading of the lesion would help to explain the day-blindness and the colour anomalies that are undoubtedly present as a congenital association in some cases and may possibly develop in others with the progress of the lesion. It is tempting to regard the macular dystrophies as the counterpart of retinitis pigmentosa, the one being a cone lesion and the other a rod lesion, but such a view appears to be contradicted by Case 2 in which retinitis pigmentosa and macular dystrophy were both present. For the ultimate solution it is better to let theory wait upon observation.

Conclusions

Macular dystrophy presents such a protean range of manifestations that the classification suggested by Behr, helpful as it has been, must be regarded as distinctly schematic. The range of ophthalmoscopic appearances extends from faint mottling of the macular zone to the picture seen in " Doyne's choroiditis," almost every possible intermediate lesion having been reported. The conception of a distinctly isolated macular lesion is not valid. There may be present, not only extensive perimacular involvement but also peripheral lesions, and some general involvement of the whole fundus is not excessively rare. One case is reported showing the association of macular dystrophy with typical retinitis pigmentosa. A rigid classification of the macular dystrophies on a chronological basis involving distinct age-groups, as postulated by Behr, is not borne out by experience. The age of incidence extends, just as the ophthalmoscopic appearances do, over a continuous unbroken range.

The apparent complexity of abiotrophic central lesions of the fundus lends itself to considerable simplification. Three clear cut types are recognisable.

(1) Central choroidal sclerosis as shown in a previous paper. Here the primary lesion develops in the vascular bed of the choroid.

(2) Angeoid streaks—which must now be regarded as part of the generalised process of elastosis dystrophica—produced by ruptures in the membrane of Bruch and followed by secondary changes.

(3) Central retinal dystrophy: Theoretically the central retinal dystrophies might show several sub-varieties: two neuro-epithelial types, in one the rods would be involved, in the other the cones; a type dependent upon degeneration of the ganglion cells; and a further type dependent upon changes in the retinal capillaries supplying the central area. On the present material and almost total lack of histological information, this fine subdivision is impossible.

Summary

(1) Eight familial groups of macular dystrophy are reported.

(2) They illustrate the great range of ophthalmoscopic appearances, extending from fine mottling of the maculae to "exudative" reactions, "inverse retinitis pigmentosa," intense central pigmentary changes, hole formation, extensive perimacular involvement and the patterned reaction of "Doyne's choroiditis."

(3) Symptomatically macular dystrophy has an equally wide range. The symptoms may be so severe as to constitute total day blindness (total colour blindness) or so mild that vision is hardly affected. The condition is not necessarily rapidly and relentlessly progressive.

(4) On the basis of these cases, supported by an analysis of the material recorded in the literature, it is held that Best's congenital macular degeneration, Doyne's choroiditis, Stargardt's disease and the numerous types of central macular dystrophy described by different observers constitute a single clinical entity with more than one mode of inheritance.

(5) This central retinal dystrophy has to be distinguished from central choroidal dystrophy (central choroidal sclerosis) and central internal limiting membrane dystrophy (angeoid streaks).

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APPENDIX

A NOTE ON THE GENETIC ASPECTS OF MACULAR DYSTROPHIES

BY

HANS GRÜNEBERG

LONDON

MR. SORSBY'S paper raises the important issue of the classification of a number of allied or partly identical inherited conditions.

The general aim of aetiological research is to base the classification of diseases not on symptoms, but on causal units. Thus in the case of infectious diseases, we aim at classifying according to the specific causal organisms. We know that, depending upon the patient's immunity and the part of the body affected, the same organism may produce a variety of clinically different pictures; and furthermore that practically identical symptoms may be caused by quite distinct bacteria. One of the reasons for preferring a causal to a symptomatic classification is that causal unities may be successfully treated by a specific causal therapy, whereas causally heterogeneous symptoms cannot be dealt with successfully.

The situation as regards inherited disease is very similar. Hereditary factors or genes are units which govern a unit process during development or later in life. Classification of inherited diseases aims at sorting them out according to the underlying unit processes. This unit process may be called the primary action of the gene, as distinct from secondary effects. Sometimes there is a whole hierarchy of secondary and tertiary effects which may be set out in the form of a " pedigree " of causes. The primary effect may be strictly localised in the body, or it may affect several structures. If several structures are primarily affected, this may be due to the fact that the gene acts on a particular tissue, wherever it occurs in the body; or to the fact that the primary effect operates at a particular time in development on several structures which at that time are specially susceptible to a change, from such conditions as humoral changes in the humoral of the embryo. An example will make this clearer. There exists an inherited condition in the rat[1] which primarily affects the cartilage, causing it to hypertrophy enormously in certain localized positions of the skeleton of the limbs, ribs, trachea, and nasal septum. In the thorax this hypertrophy leads to considerable malformation; as a consequence, emphysema of the lungs and bronchiectasis develop, and this in turn brings about tertiary effects on the pulmonary

circulation which ultimately leads to the death of the animal. That the cartilage anomaly is in fact the primary lesion has been shown by reciprocal transplantation experiments.[2] Young cartilage destined to become hypertrophied does so even in a normal host, and cartilage destined to be normal develops normally even in an abnormal animal. It is thus clear that the primary action on the cartilage is always present, whereas some of the more remote effects may or may not develop. Now, if for some reason, the primary effect of a gene were unknown, and we based our pedigree on some secondary effect, we would score some individuals as normals, although according to theory they should be affected. It is probable that " irregular manifestation " of a gene as so often observed both in man and in experimental animals and plants is always of this type. It is probably only found when we base our classification on a secondary effect of a gene.

The manifestation of genes depends on the environmental conditions in the widest sense—pre-natal and post-natal, acting from outside the body, or inside the body, such as humoral processes not governed by the gene itself. Gene manifestation is further influenced by the " genotypic milieu " or the " residual genotype," *i.e.*, the entirety of the other genes of which the body is made up. Genes interact in development, and the presence of one or more particular genes may influence the manifestations of others. In experimental material, the influence of the residual genotype or the environment can be distinguished by the effect or otherwise of selective breeding. In man, it is at present difficult to tell these two factor groups apart.

Genes often occur in several modifications, called " multiple allelomorphs." In such cases, the same normal gene has mutated in two or more different ways. The same basic mechanism is altered, but in somewhat different ways. Very often, the difference between the multiple allelomorphs is quantitative in effect. In the fruit-fly *Drosophila*, for instance, there exists a series of twelve allelomorphs which dilute the normally intensely red colour of the eye to various degrees ranging over blood, cherry, apricot, eosin, ivory, etc., down to pure white. Each of these types breeds true. If any two of them, excluding that with normal eye colour, are crossed, the result is intermediate. This intermediate behaviour of the compounds is a proof that basically the same process is affected. In some cases, the difference between the multiple allelomorphs is qualitative. The mutant truncated wings in *Drosophila* has an allelomorph which also causes the hairs of the thorax to be arranged in whirls, and a third allelomorph affects essentially only the thoracic hairs. Such cases are

common and are of considerable importance in human genetics. For instance, there exist families of autosomal recessive retinitis pigmentosa with and without deafness. Such cases might conceivably belong to a series of multiple allelomorphs, though in this particular case there is reason to believe that this is not so.[3]

In the cases mentioned, all the multiple allelomorphs were recessive in relation to the normal form. This is not always the case. Instances are known where a series of multiple allelomorphs contains genes, some of which are dominant to the normal form, and others recessive. In retinitis pigmentosa,[3] there occur families in which the gene is incompletely sex-linked; in some families the condition is recessive, in others dominant. Haldane showed that there is some reason to regard these dominant and recessive conditions as allelomorphic and therefore due to the same unit process in development; much more material would be necessary to prove this genetical identity beyond doubt. In the material presented by Mr. Sorsby, some families show an irregularly dominant type of inheritance, whereas others are recessive. This does not necessarily mean that the conditions are entirely different and due to different genetic unit processes. They may quite well belong to the same series of multiple allelomorphs. This question could only be decided by an actual cross or if a marriage took place between affected members of different families, a highly unlikely event.

The same anomaly may be produced by totally different genes. In the mouse, there are two genes, each of which causes a dilution of the fur pigments and a pink eye colour. The two types are indistinguishable in their appearance, and if such anomalies had occurred in man, they would very probably have been regarded as identical. And yet, when these two strains are crossed, entirely normal animals are produced. Evidently, two different unit processes are involved, although the end result is the same. Designating the normal genes with capitals and the recessive abnormal genes with small letters, the two strains are of the structure AAbb and aaBB respectively. The hybrid is AaBb, and as A and B are dominant over a and b, is normal. Such mimics are universal in their occurrence, and many dozens of examples could be given. One way to discover their non-identity is by crossing, but this will practically not occur in man. Another proof of non-identity comes from establishing that the two genes are carried in different chromosomes or in different loci of the same chromosome; in man, the only chromosomes that at present can be differentiated from the rest are the sex chromosomes, where the sex-differentiators serve as " markers." If both mimics are autosomal—and this will happen in the majority of cases—

they cannot be distinguished. Sometimes, a detailed histo-pathological comparison may give a hint.

It should be stressed that all the gene effects briefly indicated here, such as multiple effects of single genes, irregular manifestation of genes due to environment or the residual genotype, multiple allelomorphs and mimics, are by no means rare exceptions. They are widely spread and by far more common than inheritance in a simple Mendelian manner. With the virtual certainty that they all occur in inherited human diseases, we have to discuss whether, and to what extent, they can be distinguished in actual practice.

The problem is this: how can allelomorphism of genes be proved or excluded in human inherited disease? As already indicated the most direct way would be by crossing; if the compound were similarly affected as the two affected parents, allelomorphism would be proved; if the compound were normal, it would be excluded. This direct way is impracticable in man. Allelomorphism is also proved if it can be shown that the two genes occupy the same locus of a given chromosome, and it is excluded if it can be shown that the two genes occupy different loci of the same chromosome, or that they are carried in different chromosomes. At present, this approach has a limited value in human genetics as the only distinction possible is between sex-linked and autosomal mutants. It is to be expected that the mapping of human chromosomes will extend this possibility to individual autosomes in course of time. A detailed study of the histo-pathological development may be helpful; if it should be found that two similar anomalies occurring in two families are caused by a different pathological mechanism, this would be presumptive evidence that the two conditions are genetically distinct.

In the case of the macular lesions, no decision is yet possible. There undoubtedly exist families in which the lesions are (more or less irregularly) dominant, and there undoubtedly are families where the anomaly is due to a recessive gene (or genes), as evidenced by the high incidence of consanguineous marriages. This difference alone does not prove that the group is genetically heterogeneous, as dominant and recessive types may belong to the same allelomorphic series. On the other hand, there is no genetic proof that the group is homogeneous. The issue cannot be decided on the incomplete genetic evidence available as yet.

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ANNOTATION

Association for the Prevention of Blindness in Bengal

The Ninth Annual Report of the Association for the Prevention of Blindness in Bengal, 1938-1939, has just reached us. It shows how much has already been accomplished in a short time and makes most interesting reading. The common underlying causes of blindness in Bengal are apathy, ignorance and poverty. With the limited funds at its disposal the Association is obviously doing magnificent work and great credit must be given to the Committee and especially to its Hon. Secretaries, Lieut.-Col. E. O'G. Kirwan and Dr. S. K. Mukerjee for the immense amount of time and trouble they have taken and are taking. The number of totally blind in India is approximately one million, and the number of partially blind in India is approximately three million. There are 37,000 totally blind and 111,000 partially blind in Bengal. Sixty per cent. of blindness is preventable and universal vaccination would prevent more blindness than all the eye hospitals in India could cure.

Egypt with its population of 15,000,000 has 17 travelling eye dispensaries; India with 350,000,000 population has only two travelling eye dispensaries. The Jubilee Travelling Eye Dispensary has treated 42,761 cases in 751 working days. The Second Travelling Eye Dispensary has treated 36,396 cases in 400 working days. And these two dispensaries have so far covered only a small area. Five dispensaries are needed for the five divisions of Bengal. It is heartening to learn that the Government has sanctioned a grant for the ensuing year which will enable the Committee to put two more travelling dispensaries into commission. During the year under review the Committee has arranged for the eye examination of children in schools and orphanages in Bengal.

The propaganda work includes lectures, posters, films, publications, exhibitions, radio talks and newspaper articles with other miscellaneous items.

Some of the posters published by the Association are reproduced in the report. They include one on septic teeth; one on the essential foods to prevent keratomalacia; one on the enemies of childrens' eyes, viz.: sore eyes at birth, smallpox, keratomalacia and inherited syphilis; and one on the danger of leaning out of carriage windows on trains without wearing goggles.

Other illustrations show some of the crowds of patients waiting for treatment at the travelling eye dispensaries. Appendices contain among other items, a statement of accounts for the year, the annual budget for a travelling eye dispensary, a list of schools where lectures (Red Cross) and demonstrations have been given and the yearly report of the two travelling eye dispensaries.

It is obvious that the Association is doing splendid work. Finance is, of course, the most urgent problem; with increased resources we may expect that the Association will be able to do much towards combating a serious menace to the prosperity of the Bengal Presidency, and also the whole of India.

ABSTRACTS

MISCELLANEOUS

(1) **Blatt, Nicholas (Bucharest).—Selection of flying personnel. (Sélectionnement des aviateurs, au point de vue de leur organe visuel).** *Rev. de Service de santé militaire.* March, 1940.

(1) Good sight is essential to all the members of any flying corps but there are many points which are equally important, besides central acuity of vision. **Blatt** in this paper explains in what direction their importance lies, and how the candidate must be examined to ensure that no unsuitable man gets through.

A number of functions of the eye must be investigated; the central acuity must be normal or very nearly so; in most countries it is usual to exclude all who wear glasses, but it seems unnecessary in the author's opinion to draw the line so rigorously. He would allow low hypermetropia, so long as the vision was perfect with the correction, which should be worn always. A full field is necessary; this must be taken on a perimeter. The fundus must be examined and be normal. Light sense must be normal; a man with deficient light sense is at a grave disadvantage in a bad light and is almost a blind man. It is not easy to test the light sense; a fair judgment may be made by reducing the light reaching the eye by dark glasses and comparing the vision of the candidate with that of the examiner; if the light sense of the latter is good and the findings of the candidate agree, the candidate may be assumed to have normal sense.

Muscle balance must be good; a low exophoria is admissible but esophoria, even of low degree, may give rise to errors of judgment in estimating distances; it is therefore a bar to acceptance. Estimation of distance and stereoscopic vision must be good. Colour vision must be good; the author holds that the examination both of colour sense and central acuity, should be made out of doors, if possible under conditions of flying. Lastly, the mental agility must be examined; the pilot must be quick to receive and to interpret stimuli and to act at once on the information thus attained.

HAROLD GRIMSDALE.

(2) **Bardanzellu (Genoa).—Mercurochrome as an antiseptic in ophthalmic practice. (Un nuovo antisettico per uso locale in oculistica il mercurocromo).** *Boll. d'Ocul.*, January, 1940.

(2) **Bardanzellu** points out that all ophthalmic operations are subject to the risk of infection since it is not possible to make the field of operation aseptic. He has found mercurochrome superior to all other antiseptics for use in the eye. He uses a four per cent. solution, dropped into the cul-de-sac; if there is any obvious conjunctival inflammation he uses the drops for several days before the operation; when an operation must be performed without delay, it suffices to drop in mercurochrome three or four times at intervals after thorough washing with distilled water. He has found no inconvenience except that the drug stains the part with which it comes in contact; this stain soon is effaced. He has tested the power of the drug against various germs which are commonly met with in the conjunctiva, and has found it very efficient in curing all conjunctival inflammations and blepharitis.

HAROLD GRIMSDALE.

(3) **Anand, H. L. (India).—Entropion of the upper lid after tarsectomy; operation to correct.** *Indian Jl. of Ophthal.*, Vol. I, No. 1, p. 20, January, 1940.

(3) The author describes a method of correcting entropion resulting from an unsuccessful operation of combined excision of tarsus and trachomatous conjunctiva. While the reviewer has never experienced the need for such correction after his own operations the exposition offered by **Anand** may be of value to those who use a different technique from that described in the *Transactions of the Ophthalmological Society of the United Kingdom*, Vol. XLV, Part I, p. 90, 1925.

The operation consists of three stages:—(1) Excision of a graft from the cartilage of the ear; this is done under local anaesthesia and should be 20 mm. by 15 mm. and rather less than 1 mm. thick; when separating the skin from the cartilage care must be taken to avoid injury to the epichondrium. (2) Preparation of a bed for the cartilage; the entropion spatula is introduced under the lid, after effecting local anaesthesia, and a horizontal incision is made through the skin 4 or 5 mm. from the free border of the lid. The skin is separated from the underlying tissue above and below (to the very edge of the lid). The graft is then laid in the bed made for it with the epichondrium uppermost. (3) Insertion of sutures; three loop sutures are inserted in the tissue of the lid above the graft, each taking a bite of tissue; each one then takes a bite of the epichondrium of the graft and is then inserted through the strip of tarsus remaining in the free border of the lid and brought out among the

lashes; each pair is tied over a fragment of cotton wool, and the ends are drawn upwards and fixed to the forehead with plaster. The skin wound is closed by a few sutures. Two or three sutures are used to close the wound of the ear. All sutures may be removed on the fifth day.

A. F. MACCALLAN.

(4) **Thies, O. (Dessau).—Chemical injuries of the eye. (Der Verätzungen des Auges).** *Klin. Monatsbl. f. Augenheilk.*, 1938.

(4) This monograph of 100 pages is an important contribution which should receive the careful attention of all ophthalmologists who may have to deal with chemical burns of the eyes. It is well produced and is illustrated with photographs which show the grosser features of these blinding catastrophes; but in some of the illustrations it is impossible to distinguish the finer details of the damaged eyeballs.

Thies has had an extensive experience of these injuries in one of Germany's centres of chemical industry, and he is an advocate of *immediate* surgical intervention in all cases of any severity; the operation advised is the excision of all the ocular conjunctiva involved close up to the limbus, and thorough removal of episcleral tissue, and the covering of the defect by a sufficiently large mucous graft from the lip.

The paper in addition to the surgical suggestions covers several aspects of the subject, historical, chemical, pathological and clinical.

The method was originally devised by Denig.

The severity of the burn depends on five factors:—(1) the chemical nature of the poison, (2) its concentration, (3) its amount, (4) the duration of its effect, (5) the force of impact.

The chemical action may be (1) immediate, when it acts primarily on the connective tissue and its contained albumen, or (2) delayed, the albumen of the tissues forming an albuminate with the poison. This product diffuses more deeply into the tissues and causes progressive damage by destroying the episclera and even the sclera and the nutritional zone of vessels around the cornea. Such delayed action explains the corneal opacification which may appear several days after this type of injury. Such opacity is permanent and may progress even to perforation.

Three degrees or stages of burn on the eyeball are described. The first is mild, with conjunctival reaction, little or no chemosis and a practically clear cornea. The second shows chemosis, usually below, with perhaps some corneal change. Opacity and ulceration may occur from inanition later. In the third type, the tarsal conjunctiva may be necrotic, the bulbar conjunctiva is at first chemosed and firm, but will show areas of necrosis, and may be porcelain

white and shredded. The cornea becomes progressively more hazy, and is insensitive. Later the cornea and even the sclera may necrose.

The various chemicals involved and their several actions on the tissues are considered in detail. It is pointed out that acids precipitate the albumen of the surface cells, and do not tend to extend deeply apart from the initial mass of chemical and the penetrating force of the injury. On the other hand, alkalis and ammonia (the latter from ice making machines) form anhydrous albuminates which abstract water and spread deeply. Lime burns too impregnate deeply, especially if the particles have been forced inwards and necrosis is caused around them. Other poisons such as turpentine, aniline dyes, alcohol, corrosive sublimate, war gases and sulphuretted hydrogen are also considered.

Therapy is discussed in minute detail in respect of the lesions in the lids and face and in the eyes themselves. With regard to the skin, the author is in favour of conservative treatment until the active stage is passed, unless keratitis from exposure is threatening. For plastic work he favours pedunculated flaps of the Imre circular type. He appears not to favour Thiersch grafts, but to approve the application of free grafts involving the whole thickness of the skin in the upper lids but not in the lower.

The initial first aid treatment to the eyes should be flushing with water; but from experience and from experimental evidence obtained from animals it is probable that no effect results from any applications after the first few minutes or even seconds.

In mild cases the application of liquid paraffin, the removal of solid particles and the use of a glass rod to prevent adhesions are advised.

The main theme is the application of early lip graft to replace the damaged conjunctiva, and his arguments in favour of this being done at the earliest possible moment are attractive. Denig since 1904 has advocated the method, and more vigorously with increasing experience. The chemical poisons seem to condense in places and extend deeply into the episclera producing reaction, necrosis and obliteration of the marginal vessels with resultant corneal degeneration. By removal of all this area and replacement with healthy mucosa, a re-establishment of the peripheral corneal nutrition is said to occur, the corneal opacity does not progress and symblepharon does not materialise. It is advocated in all severe cases when the conjunctiva is markedly damaged, certainly always in 3rd degree cases and usually in 2nd degree cases. Corneal anaesthesia and involvement, porcelain-like opacity of the conjunctiva or a patchy necrosis are the chief indications.

Publications by a number of operators who have followed Denig are quoted, giving satisfactory results; and a summary is given of

the experimental work on animals which bears out the theory of the deep spread of the chemicals in the tissues.

The time for the grafting should be as early as possible, as soon as the severity of the case is certain. Delay only permits the extension of the deep chemical action, and the continuance of corneal malnutrition.

The operation is usually performed under local anaesthesia as this stops the tendency to chest complications from oral haemorrhage.

All necrotic and damaged conjunctiva is removed and the underlying episclera must be carefully dissected away, right down to the sclera. It is also stressed that the area must be cleared well up to the limbus, and into healthy surrounding conjunctiva.

The lip graft is then prepared. Novocain 2 per cent. or 1 per cent. with adrenalin is injected under the mucosa over a sufficiently wide area, and a large lip clamp encircles the part for dissection, so that haemorrhage is under control. The graft should be nearly twice the size of the conjunctival bed. It is outlined by a knife, and is dissected off by angled scissors. The gap in the lips is closed by several sutures. In extensive cases two grafts may be needed, to be placed above and below the cornea.

The separated graft is then freed of all fat by cutting this away with curved scissors until it is uniformly thin. It is important to do this thoroughly, but punctures should be avoided.

The edge of the graft is attached to the conjunctiva and episclera by fine sutures, and the graft must be flat without folds or underlying clot. The corneal border must be free and trimmed to shape.

Both eyes should be bandaged for four days, the pads to be changed daily if necessary, but are best left alone.

Complications are said to be unusual if the technique is correct. Sufficient excision of necrotic tissue is very important, both superficially and deep. The author states that sloughing of the graft from suppuration does not occur.

F. A. JULER.

BOOK NOTICE

Some Clinical Aspects of the Ocular Involvement in Lepers. By JOSÉ MENDONÇA DE BARROS. Companhia Melhoramentos De Sao Paulo, Rio de Janeiro.

The incidence of leprosy in this country is unknown, for the disease is not notifiable. It is certain, however, that there are a considerable number of such patients, particularly in the larger seaport towns, and, as the incidence of ocular involvement is high,

that many of them will gravitate not infrequently to eye hospitals and clinics.

English speaking ophthalmic surgeons owe a considerable debt to José Mendonça de Barros for appending an adequate and readable translation to his monograph on the "Clinical Aspects of the Ocular Involvement in Lepers." This work emanates from the prophylactic service against leprosy in the State of Sao Paulo, Brazil, and is the result of observation on some 1,200 patients.

The lids, surrounding skin and anterior segment of the eye are dealt with in a routine manner, and the results of wide experience and meticulous examination are evident, more particularly in the slit-lamp observations on the cornea and iris.

This monograph is of limited scope, and many aspects of ocular leprosy are not touched upon. In particular the views of the author would be welcomed on the indications for the surgical removal of the episcleral leproma and the results to be anticipated in the eye of modern therapeutic measures.

Thirty-one coloured plates, both photographs and drawings, of outstanding excellence, will perhaps prove the most useful features to those surgeons rarely in contact with this disease. They convey in a lucid manner both the naked eye and slit-lamp appearances of the pathognomonic changes characteristic of leprosy in the skin, sclera, cornea and iris. A number of monochrome photographs are also included, but these are much less effective in conveying the clinical picture.

This short work can be cordially recommended to all engaged in the practice of ophthalmology.

FUTURE ARRANGEMENTS

1940

October 19, 1940.—North of England Ophthalmological Society, at Manchester.

November 16, 1940.—North of England Ophthalmological Society, at Bradford.

December 14, 1940.—North of England Ophthalmological Society, at Leeds.

1941

February 1, 1941.—North of England Ophthalmological Society, at Newcastle-on-Tyne.

March 1, 1941.—North of England Ophthalmological Society, at Liverpool.

March 29, 1941.—North of England Ophthalmological Society, at Sheffield.